Archives of Neurology and Psychiatry

VOLUME 38 SEPTEMBER 1937 NUMBER 3

HYPOTHALAMIC REGULATION OF TEMPERATURE IN THE MONKEY

S. W. RANSON, M.D.

C. FISHER, PH.D.

AND

W. R. INGRAM, PH.D.

CHICAGO

The location of the temperature-regulating center has formed the subject of many investigations. The work of Isenschmid and Schnitzler [1] has given what seems to us reliable information. They showed that small bilateral lesions in the region of the mammillary bodies and the posterior part of the tuber cause loss of the capacity to guard the body against abnormal drops in body temperature. More recent work has established beyond dispute the importance of the hypothalamus for regulation of temperature, but there is a great deal of difference of opinion as to the exact location of the center or centers involved (Alpers; [2] Bazett, Alpers and Erb; [3] Bazett and Penfield; [4] Davison and Selby; [5] Dworkin; [6] Frazier, Alpers and Lewy; [7] Glaubach and Pick [8] Keller: [9] Keller and Hare, [10] and Solari [11]).

From the Institute of Neurology, the Northwestern University Medical School.

This investigation was aided by grants from the Rockefeller Foundation and from the Ella Sachs Plotz Foundation.

1. Isenschmid, R., and Schnitzler, W.: Beitrag zur Lokalisation des der Wärmeregulation vorstehenden Zentralapparates im Zwischenhirn, Arch. f. exper. Path. u. Pharmakol. **76**:202, 1914.

2. Alpers, B. J.: Hyperthermia Due to Lesions in the Hypothalamus, Arch. Neurol. & Psychiat. **35**:30 (Jan.) 1936.

3. Bazett, H. C.; Alpers, B. J., and Erb, W. H.: Hypothalamus and Temperature Control, Arch. Neurol. & Psychiat. **30**:728 (Oct.) 1933.

4. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as in the Acute Condition, Brain **45**:184, 1922.

5. Davison, C., and Selby, N. E.: Hypothermia in Cases of Hypothalamic Lesions, Arch. Neurol. & Psychiat. **33**:570 (March) 1935.

6. Dworkin, S.: Observations on the Central Control of Shivering and of Heat Regulation in the Rabbit, Am. J. Physiol. **93**:227, 1930.

7. Frazier, C. H.; Alpers, B. J., and Lewy, F. H.: The Anatomical Localization of the Hypothalamic Centre for the Regulation of Temperature, Brain **59**:122, 1936.

(Footnotes continued on next page)

Observations made on animals decerebrated at various levels are not altogether satisfactory because so much of the brain is removed, because the preparations thus obtained differ greatly from a normal animal and because parts of the brain stem remaining in place may have been rendered functionless by anemia, hemorrhage and inflammatory reactions. However, when temperature control is retained after transection of the brain, it is safe to conclude that the parts removed are not essential for this function. It is reasonable to expect that lesions placed in the hypothalamus with the Horsley-Clarke apparatus will furnish more reliable information because the lesions are sharply defined, while all the rest of the brain is left undamaged, and because such animals can be kept and studied for as long as desired and are normal except for the disturbances in temperature control, changes in emotional reactions and a tendency to drowsiness, all of which symptoms result directly from the hypothalamic lesions. Most investigations of this problem in the past have dealt with acute preparations or with animals which lived but a few days. The best animal in the investigation reported by Frazier, Alpers and Lewy [7] survived only five days.

It is possible that there may be subsidiary centers for temperature control in the medulla (Keller [9]) and the spinal cord, and evidence in favor of this is seen in the recovery in the course of time of some capacity for maintaining a normal body temperature after transection of the cervical portion of the spinal cord (Thauer [12]). Observations of this sort, however, in no way invalidate the evidence pointing to the hypothalamus as the site of the chief mechanism responsible for thermostasis.

METHODS

Young Macacus rhesus monkeys weighing from 3 to 6 pounds (1.3 to 2.7 Kg.) were used. Lesions were placed bilaterally in the hypothalamus, with the aid of the Horsley-Clarke stereotaxic instrument. Unipolar electrodes were used, with the indifferent electrode in the rectum. As a rule, each lesion was produced by a current of 3 milliamperes passing for sixty seconds. Several lesions were made along each puncture. Sometimes one and sometimes two punctures were made into each side of the hypothalamus. When two punctures were made, they were placed 1 mm. apart, one in front of the other. Practically all punctures were made

8. Glaubach, S., and Pick, E. P.: Ueber zentrale Temperaturregulierung nach Ausschaltung des hypothalamischen Wärmzentrums, Arch. f. exper. Path. u. Pharmakol. **173**:571, 1933.

9. Keller, A. D.: Observations on the Localization in the Brain Stem of Mechanisms Controlling Body Temperature, Am. J. M. Sc. **185**:746, 1933.

10. Keller, A. D., and Hare, W. K.: Heat Regulation in Medullary and Mid-Brain Preparations, Proc. Soc. Exper. Biol. & Med. **29**:1067, 1932; The Hypothalamus and Heat Regulation, ibid. **29**:1069, 1932.

11. Solari, L. A.: Température et réactions thermiques chez les chiens hypophysoprives ou à tuber lesé, Compt. rend. Soc. de biol. **108**:125 (Oct. 12) 1931.

12. Thauer, R.: Wärmeregulation und Fieberfähigkeit nach operativen Eingriffen am Nervensystem homoiothermer Säugetiere, Arch. f. d. ges. Physiol. **236**:102, 1935.

2.5 mm. from the midline. The monkeys were under pentobarbital sodium anesthesia. The operations were performed aseptically, and no infection of wounds occurred.

Most of the animals which showed a tendency to have a subnormal temperature were kept for a time in an incubator regulated at from 84 to 86 F., but some were kept from the start under ordinary room conditions. Readings of the rectal temperatures were made each morning until the animals had thoroughly recovered. At the same time, a record was made of the temperature of the room, if the animal was not in the incubator. The room temperature did not fluctuate rapidly, since it was an inside room, without windows or radiators. To insure ventilation, air was drawn out through an opening near the ceiling, and the room was heated only by the air drawn in through the door from a central hallway. During the night the door was closed and the ventilating fan stopped, and since readings of rectal and room temperatures were made in the morning, the recorded room temperature may be taken as accurately representing that of the preceding fifteen hours.

The animals were kept under observation for many days or weeks. They were finally killed by exsanguination, and the brain was injected through the arteries with a solution of formaldehyde U. S. P. (1:10). Serial sections were cut of the part of the brain containing the lesions, and sections were stained alternately with cresyl violet and the Weil method.

RESULTS

Regulation of Temperature in the Normal Monkey.—Before a description is given of the behavior of the body temperature of the monkeys on which operation was performed, a brief discussion of temperature regulation in the normal monkey will be presented, for it is only by comparison with the normal that deviations can be detected.

It was found that the normal temperature of the monkey is quite inconstant, varying from about 101 to 103.5 F. The monkeys in our series were rather wild and frequently put up a hard struggle before they permitted themselves to be caught and held for the insertion of the thermometer. This struggling was found to increase the body temperature. In order to obtain a closer approximation to the normal, three monkeys were strapped into hammocks and the rectal temperatures followed over a period of about seven hours, at a room temperature which varied from 80.6 to 82.4 F. The accompanying tabulation gives the results.

Monkey No.	Temperature at Beginning of Experiment, Degrees F.	Temperature at End of Experiment, Degrees F.
N 17	102.6	100.1
N 18	102.4	100.7
N 19	103.0	101.6

It usually happens that a wild monkey will lie quietly after it has been caught and strapped in the hammock. This was true in the case of the first two monkeys, but the third remained rather active and struggled considerably. It should be noted that the drops in temperature recorded in the table took place in a warm room. From this experiment

it may be concluded that the rectal temperature of the normal monkey varies from 100 to 101.5 F. and that the temperatures which are registered immediately after a monkey is caught are generally too high (Kennard [13]).

In order to study the effects of exposure to lower temperatures, the eight normal monkeys listed in table 1 were placed in a room which was cooled to around 65 F.

The period of exposure lasted in most cases about three hours. For the eight monkeys an average decrease in temperature of 2.53 F. occurred. It should be noted, however, that the temperatures of these animals before exposure to the cold were fairly high and that, judging from the responses of the three normal monkeys which were strapped in a hammock and exposed to room temperature for seven hours, part of the decrease would have taken place if these eight animals had been exposed to room temperature instead of to a lower temperature. Conservatively, the decrease due to the chilling may be estimated at 1.5 F. Although the rectal temperature in no case fell below 98.1 F. and the external temperature was not low, shivering was noted in six of the eight experiments. In connection with this shivering at moderate room temperature, it should be remembered that the rectal temperature had previously been elevated slightly, as a result of struggling.

TABLE 1.—*Decreases in the Rectal Temperature of Normal Monkeys When Exposed to Moderately Low Temperatures*

Monkey No.	Rectal Temperature Before Exposure to Cold, Degrees F.	Rectal Temperature After Exposure to Cold: Time Elapsed	Rectal Temperature After Exposure to Cold: Temperature, Degrees F.	Temperature of Cold Room, Degrees F.	Total Drop, Degrees F.	Shivering
N5 MC36*	102.5	3 hr. 30 min.	101.4	65	1.1	Marked
N6 MC37	101.8	3 hr.	100.6	66	1.2	Present
N11 MC38	101.4	3 hr.	99.6	66	1.8	Slight
N12 MC39	101.7	3 hr. 30 min.	98.1	63-68	3.6	Marked
N13 MC40	102.7	3 hr.	99.1	65	3.6	None
N14 MC41	103.3	3 hr.	100.4	70.5	2.9	None
N15 MC42	102.2	3 hr. 30 min.	98.4	63-68	3.8	Marked
N16 MC43	102.6	2 hr. 35 min.	100.4	62-63	2.2	Moderate
Average					2.53	

* Lesions were subsequently placed in the brain of each of these monkeys. The numbers preceded by MC are those by which the animals were designated after the operations.

The effect of subjecting normal monkeys to high external temperatures was studied in two sorts of experiments. In an earlier series four normal animals were placed in a heating box, measuring 30 by 24 by 12 inches (76.2 by 60.96 by 30.48 cm.), which was kept at a temperature of from 102 to 104 F.

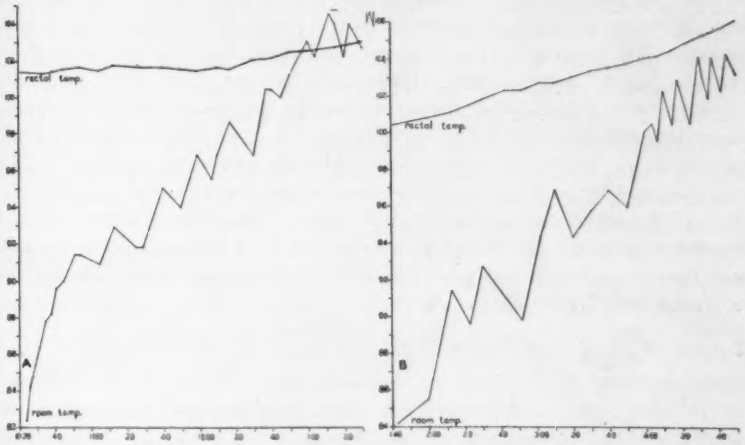
We were surprised to see that on exposure to moderately excessive heat the rectal temperature began to ascend rapidly, reaching in some instances 106 or 107 F., a point beyond which it was never forced. This rise was not due to

13. Kennard, M. A.: Corticospinal Fibers Arising in the Premotor Area of the Monkey, Arch. Neurol. & Psychiat. **33**:698 (April) 1935.

excitement and struggling caused by restraint in the hammock. In fact, as already mentioned, monkeys rest rather quietly in the hammock, and under ordinary room conditions the rectal temperature falls below the point at which it stood when the animals had just been caught.

Some increase in the rate of respiration accompanied the increase in rectal temperature. This increase might have been greater had not the rate been high to start with, owing to excitement. In most cases no marked increase in rate occurred until the rectal temperature became high. The greatest increase recorded was 61 per minute, an increase from 64 to 125 a minute. The monkey does not pant. Sweating was not profuse.

As an additional test, it was decided to subject the monkeys to gradually increasing temperatures, starting from 82 to 86 F. and gradually increasing to 104 F., over a period of several hours.



A B

Chart.—*A* shows rectal and room temperatures, expressed in degrees Fahrenheit, plotted against time, in an experiment on normal monkey 17. The room, or more properly, the box temperature was raised more than 10 F. in three hours, with only an insignificant rise in rectal temperature. *B* shows rectal and room (box) temperatures, expressed in degrees Fahrenheit, plotted against time, in an experiment on monkey MC 31. The rise in rectal temperature began early and continued steadily throughout the experiment.

Four normal animals (N 12, 17, 18 and 19) were gradually warmed in the manner indicated. Three of the four monkeys maintained fairly steady temperatures until the box reached 100 or 102 F., when the rectal readings began to rise. One of the four showed a slight increase, which began when the box reached 98.6 F. (chart *A*). In three of the four monkeys marked sweating occurred, more profuse than anything which had been noted in the earlier experiments, when the monkeys were exposed immediately to a temperature of from 102 to 104 F. In the fourth animal (N 12) there was less marked sweating; only dampness of the palms and soles was observed.

From all these observations it can be seen that the monkey does not possess a stable or efficient temperature-regulating mechanism. Normally the temperature varies over a range of several degrees and frequently shows increases as a result of emotional excitement or struggling. At external temperatures which are only moderately low, from 64 to 68 F., a slight drop may occur in the rectal temperature. Finally, under the conditions of our experiments the normal monkey does not compensate well for temperatures as high as 102 F. Sherrington [14] also noted that monkeys do not react well to high temperatures.

For our purposes it was important to know how far pentobarbital sodium, used as the anesthetic for the operations, interfered with heat regulation.

In order to test this, three normal monkeys were given doses of pentobarbital sodium equivalent to those administered to the monkeys on which operation was performed. The monkeys were strapped in hammocks, and the pentobarbital sodium was injected intravenously, at about 10:30 a. m. The rectal temperature was then followed until 5:30 in the afternoon. In the case of two of the animals the rectal temperature continued to fall until about 1 p. m., when it reached 97.6 F., in each instance. From this point it began to rise, without the application of the heating pad, and by 4:40 p. m., in the case of one monkey, and by 3 p. m., in the case of the other, had reached normal limits. The rectal temperature of the third monkey never fell below 98.2 F., and by 2 p. m. a normal level was attained without heat having been applied. The room temperatures during these experiments varied from 76 to 78 F.

Impaired Heat Regulation as Evidenced When Monkeys with Hypothalamic Lesions Were Kept in a Moderately Warm Room (from 70 to 86 F.).—Eight of the monkeys with hypothalamic lesions showed marked postoperative rises in the temperature, which returned to normal within a day or two. Another group was unable to keep the temperature up to the normal level. The animals in the second group were poikilothermic and were unable to protect themselves against excessive heat. If one puts aside, for the moment, the dual nature of the loss in capacity for heat regulation, it will be convenient to speak of the first group as showing hyperthermia and the second hypothermia. Of the twenty-nine monkeys with hypothalamic lesions the records for which contained reasonably adequate data on temperature, eight showed hyperthermia after operation, thirteen more or less prolonged hypothermia and eight no significant deviations from normal, when kept in a moderately warm room. This last group of animals certainly had no marked loss in the capacity to regulate body temperature, but since many of them were not subjected to either low or high temperatures, it is not possible to

14. Sherrington, C. S.: Notes on Temperature After Spinal Transection, with Some Observations on Shivering, J. Physiol. **58**:405, 1924.

say that their heat regulation was normal. They will, therefore, be left out of account in the subsequent analysis, except for four (monkeys MC 36, MC 37, MC 38 and MC 41), in which the responses to more extreme temperatures were studied.

Hypothermia.—From the time the operations were completed, about noon, until late afternoon, the rectal temperature was taken at frequent intervals. In the animals in which the lesions were so placed as to produce hypothermia, loss of heat regulation developed on the afternoon following the operation, as is shown by the data for monkey 42. The operation in this monkey was finished at noon. The room temperature throughout the afternoon varied from 77 to 78.8 F. By application of a heating pad the animal was kept warm until 3:25 p. m., when its temperature registered 99 F. The heating pad was then removed, and two and one-half hours later the rectal reading was 97.4 F. Thus, in contrast to the behavior of normal monkeys under corresponding doses of pentobarbital sodium, as described in a preceding paragraph, these monkeys continued to lose heat rapidly throughout the afternoon and required the application of external heat. In four of the animals (monkeys 36, 37, 38 and 41) in which hypothermia did not develop, the subnormal temperature due to the pentobarbital sodium disappeared, and regulation was reestablished during the afternoon.

Table 2 gives an idea of the intensity and duration of the hypothermia in a few representative experiments. The days indicated in column 2 are the number of days after operation; i. e., the first day is recorded as the day following the operation. Most of the animals were kept in an incubator (from 84 to 86 F.) during the days immediately following the operation. In column 3 of the table is shown the rectal temperature taken immediately after removal of the animal from the incubator, in which it had been uninterruptedly for at least fifteen hours. In the later experiments the animals were left in the room, and it was found that they stood such exposure well, even with rectal temperatures varying from 90 to 95 F. The temperature of the room is shown in parentheses in column 4, and the duration of the exposure, expressed in hours, in column 5. In the earlier experiments the monkeys were removed from the incubator on numerous occasions for short periods of exposure to room temperature. In order to conserve space, only a few observations have been included in the table, which, however, adequately represents the nature of the results obtained.

Table 2 contains three types of evidence of hypothermia. First, in some instances on the days immediately following operation, the rectal readings were subnormal, in spite of the animals being in the incubator. Second, on removal of the animal from the incubator for one or more hours, the rectal temperature fell, often rather precipitously. Third, some of the monkeys were left out in the room for one or more days, and during this period the rectal readings were constantly low. It is important to note that the lowest room temperature recorded in the table was 71.6 F. and that it was more often 75 F. or above. The inability to maintain normal body temperature under such conditions is evidence of severe disturbance of the heat-regulating mechanism.

As has been said, there was clear evidence of hypothermia on the afternoon of the day of operation. This condition persisted for varying

lengths of time, but for many days in practically every case. Several animals showed progressive increase in the intensity of the hypothermia during certain periods. Monkey 42 ran a fairly normal temperature in

TABLE 2.—*Temperature of Monkeys with Hypothalamic Lesions*

Monkey	Day After Operation	Rectal Temperature, Degrees F. In Incubator	Rectal Temperature, Degrees F. In Room	Hours at Room Temperature	Change in Temperature, Degrees F.
20	1	97.8	95.8 (77.0)†	2.5	−2.0
	2	97.4			
	6	101.0	95.0 (76.1)	7	−6.0
	19	101.5	101.0 (77.0)	8	+0.5
	34	.....	97.0 (77.4)	72	
	64	99.4	99.6 (77.0)	7.5	+0.2
25	1	99.9	97.4 (76.1)	0.75	−2.5
	6	95.8			
	17	101.2	95.8 (76.6)	6.75	−5.4
	38	100.0	98.5 (71.6)	7	−1.5
38	1	101.4	100.8 (77.0)	3.75	−0.6
	3	98.0	98.0 (75.2)	1.5	0.0
	10	.....	100.2 (74.3)	6	
39	2	97.4	95.8 (77.0)	1	−1.6
	9	97.0	94.7 (75.2)	7	−2.3
	10	.....	93.2 (75.2)	24	
	11	.....	88.1 (75.2)	48	
	18	98.1			
	21	.....	93.9 (78.8)	72	
	26	.....	96.1 (82.4)	192	
	33	.....	100.4 (81.9)	360	
	35	.....	102.0 (81.7)	408	
	40	.....	106.0*(78.1)	528	
40	1	.....	97.4 (78.8)	24	
	3	102.2	98.0 (75.2)	5	
	7	.....	94.6 (75.4)	24	
	8	.....	92.5 (73.4)	48	
	11	.....	90.5 (74.1)	120	
	14	.....	93.7 (75.2)	192	
	15	.....	96.4 (77.0)	216	
	20	.....	101.8 (78.8)	336	
	30	.....	102.1 (80.6)	576	
41	1	.....	101.6 (78.8)	24	
	4	.....	101.5 (74.3)	96	
	8	.....	101.0 (74.3)	192	
42	2	99.9			
	3	99.5			
	4	99.3			
	5	97.8			
	6	97.7			
	7	.....	96.5 (73.4)	24	
	9	.....	94.0 (74.1)	72	
	11	.....	92.8 (75.2)	120	
	13	.....	95.2 (77.0)	168	
	20	.....	99.0 (79.5)	336	
	28	.....	101.5 (80.6)	528	
43	1	.....	98.0 (77.0)	24	
	2	102.8			
	3	101.7			
	4	.....	93.2 (75.4)	24	
	6	.....	92.8 (73.4)	72	
	8	.....	95.0 (74.1)	120	
	15	.....	95.8 (76.5)	288	
	18	.....	99.5 (79.7)	360	

* Infection following operation on cerebellum three days before.
† The figures in parentheses represent room temperature.

the incubator for the first four days, but the rectal readings fell to 97.8 and 97.7 F. on the fifth and sixth days, respectively. The animal was then removed from the incubator, and the temperature fell progressively during the next five days, reaching 92.8 F. on the eleventh day,

after which the rectal readings began to rise again, reaching normal on the twenty-eighth day.

The ability to maintain the normal warmth of the body was greatly impaired in these monkeys. This was especially evident in the case of monkey 39. On the ninth day his rectal temperature was 97 F., immediately after removal from the incubator. He was set out in the room; in twenty-four hours the rectal reading had fallen to 93.2 F., and after forty-eight hours, to 88.1 F., although the room temperature was high (75.2 F.). Since blisters had developed on the fingers and toes from clinging to the side of the cage, the animal was put back in the incubator, where the fingers and toes healed. On the eighteenth day the rectal reading, immediately after removal from the incubator, was 98.1 F. The animal was set out in the room again, and in seventy-two hours the rectal temperature had fallen to 93.9 F., at a high room temperature (78.8 F). From this time the rectal temperature rose gradually, reaching normal on the thirty-third day. On the thirty-seventh day operation was performed on the cerebellum, and the temperature rose on the fortieth day to 106 F. Study of the sections revealed the cause of this sudden rise in temperature to be acute infection. It is interesting to note that this monkey responded to intracranial infection with a normal febrile reaction. This occurred in spite of the fact that his capacity to regulate the temperature against cold was far from normal. It is true, as shown in table 2, that he had recovered sufficiently that he could maintain a normal body temperature in an atmosphere registering 81.9 F. But when on the thirty-sixth day, i. e., on the day before operation on the cerebellum, he was put into a room at 64 F., the rectal temperature fell 8.2 degrees in three hours, from 102.6 to 94.4 F.

In all monkeys which were kept for sufficiently long periods, there was eventual recovery from the hypothermia; that is, a point was finally reached at which the animal was able to maintain a normal rectal temperature under ordinary atmospheric conditions, i. e., in air free from drafts, at about 75 F. Recovery to this extent occurred on the nineteenth day in monkey 43, on the twentieth day in monkey 40, on the twenty-second day in monkey 42 and on the thirty-third day in monkey 39. In the other monkeys the data on this point are incomplete, but it is known that the hypothermia persisted for more than thirty days in monkeys 20 and 25 and for about twenty days in monkeys 21 and 22. When such animals were exposed to cold, however, it became apparent that recovery was far from complete.

Observations made on animals with hypothalamic lesions in which hypothermia had never developed may be cited. In monkey 36 slight hyperthermia developed on the afternoon of the operation, the rectal temperature reaching 104.5 F., at 6 p. m. On the days following the

operation the rectal readings were normal, although the animal was not kept in the incubator. Monkey 37 maintained a rectal temperature of 99 F., in a room at 75.2 F., on the afternoon following the operation, and the same rectal reading was recorded on the fourteenth day, in a room at 77 F. Monkey 38 had a rectal temperature of 100.2 F. on the fourth day after operation, in a room registering 77.9 F. These data are sufficient to show that the capacity to maintain a normal body temperature under ordinary room conditions was never seriously impaired in these animals. When these animals were exposed to slightly lower temperatures, however, their regulating mechanism broke down.

TABLE 3.—*Decreases in Rectal Temperature of Monkeys on Which Operation Was Performed When Exposed to Moderately Low Temperatures*

Monkey	Days After Operation	Rectal Temperature Before Exposure to Cold, Degrees F.	Rectal Temperature During Exposure to Cold: Time Elapsed	Rectal Temperature During Exposure to Cold: Temperature, Degrees F.	Temperature of Cold Room, Degrees F.	Total Drop, Degrees F.	Shivering
MC31	29	99.1 I	3 hr. 40 min.	94.0—	65	5.1+	None
	43	101.7 I	5 hr.	93.7	63	8.0	Marked
MC36	3	99.1	3 hr.	95.0	66	4.1	None
	38	101.0	3 hr. 30 min.	95.0	66	6.0	Fair
MC37	2	100.3	3 hr.	95.0	66	5.3	None
	6	100.1	2 hr. 30 min.	94.1	62	6.0	Fair
MC38	3	98.6	2 hr. 30 min.	94.4	60.5	4.2	None
	22	101.5	4 hr. 10 min.	98.6	63	2.9	None
MC39	36	102.6	3 hr.	94.4	64-65	8.2	None
MC40	22	102.3	4 hr. 30 min.	96.6	64	5.7	Moderate
MC41	6	102.7	2 hr. 30 min.	99.0	65	3.7	Moderate
	17	101.6	4 hr. 10 min.	99.8	63	1.8	None
MC42	22	101.7	3 hr. 35 min.	97.8	66	3.9	None
MC43	19	101.7	4 hr. 35 min.	92.6	64	9.1	None

Impaired Heat Regulation as Evidenced When Monkeys Were Exposed to Moderately Low External Temperatures.—Animals which had passed through the period of hypothermia and were running normal temperatures lost heat rapidly when exposed to moderately low temperatures. This was true also of three animals (monkeys 36, 37 and 38) which never showed real hypothermia under the usual room conditions. The results of these tests are summarized in table 3. It should be noted that in eight instances similar tests were made on the same animals before the operation, with results that have been recorded in table 1. A comparison of these two tables will show that the drop in temperature was much more marked after lesions had been placed in the hypothalamus. Except monkey 31, which was removed from the incubator for the cold test (indicated by the letter "I" after the readings of the initial temperatures), the monkeys on which operation had been performed were being kept under ordinary room conditions. While under these condi-

tions, the thermoregulatory apparatus was adequate; it failed when the animals were subjected to somewhat lower temperatures. Although the room in which they were placed was only moderately cool (from 63 to 66 F.), the rectal temperatures fell rapidly—6 F. in three and one-half hours, in monkey 36; 8.2 F. in three hours, in monkey 39, and 9.1 F. in four and one-half hours, in monkey 43. These drops occurred in animals which had been subjected to hypothalamic injury many days before and which were in good health at the time of the test.

Although, as table 1 shows, normal monkeys do not shiver with absolute regularity when the rectal temperature falls as a result of exposure in a cool room, table 3 gives evidence that shivering was less easily induced in the monkeys with relatively slight disturbance in temperature regulation than in the normal animals. It is more significant that during the period of most marked hypothermia monkeys 39, 40, 42 and 43, when kept under ordinary room conditions, showed no evidence of shivering, even with rectal temperatures ranging from 88 to 95 F. Other monkeys which were kept in the incubator and exposed only to room temperature for short periods failed to shiver, even when the rectal temperature dropped as low as 94 or 95 F. These observations show that when the mechanism that protects the animal against cold is seriously impaired, shivering is not induced by low body temperature.

Impaired Heat Regulation as Evidenced When Monkeys Were Exposed to Moderately High External Temperatures.—Some of the monkeys with hypothalamic lesions were placed in a box which was kept at from about 102 to 104 F. The rectal temperature rose rapidly, as it did under the same conditions in the normal monkey. Indeed, little difference could be detected in the behavior of the two series, except that the monkeys which had undergone operation were never observed to sweat.

When, however, the animals were subjected to gradually increasing box temperatures, starting at from about 82 to 86 F., it became evident that the animals with hypothalamic lesions were less resistant than the normal animals. Six monkeys on which operation had been performed were exposed to the same box temperatures and for similar periods as were the four normal animals. The graph of the record obtained from monkey MC 31 (chart *B*) illustrates the nature of the response. In each case the rectal temperature rose fairly steadily throughout the period that the animal was in the warm box, in contrast to the fairly stable temperature of the normal monkey during the initial period of the heating (chart *A*). Two of the six animals tested in this way were running subnormal temperatures under ordinary room conditions. Monkey MC 39 was tested on the first postoperative day, when its temperature rose from 95.5 to 105.0 F., in four and one-half hours. The

temperature of monkey MC 43, tested on the twelfth postoperative day, rose from 94.5 to 105.3 F., in four hours. The other four monkeys were running normal temperatures under ordinary room conditions on the day when they were subjected to the test (MC 31, on the forty-eighth postoperative day; MC 38, on the twenty-fourth postoperative day; MC 41, on the fifteenth postoperative day, and MC 42, on the twentieth postoperative day). In these animals, since the initial temperature was higher, the rise was not so great, but it amounted to 3.5 or 4 F. In the six monkeys on which operation had been performed, the rise was steady and continued throughout the period of the test, while under the same conditions heat regulation in the normal monkeys functioned well until the temperature of the box reached from 102 to 104 F. While in none of the four normal animals did the temperature rise above 103 F., in each of the six animals which had undergone operation it rose to 105 or 106 F. In three of these six experiments it was necessary to remove the animal when the box reached a temperature of 99 or 100 F., for the rectal temperature had already reached 105.6 F. or above.

In none of the animals in the operative series was sweating detected. The greatest increase in the rate of respiration was from 20 to 44, an increase of 22 per minute. Two of the four normal monkeys showed greater increases than this, but the rate of respiration varied so much from animal to animal and was so largely determined by excitement that no clear difference could be determined between the normal monkeys and those on which operation had been performed. Both showed increases in the rate as the temperature of the box was raised; the smallest increase (from 42 to 44) and the greatest (from 60 to 120) were seen in normal monkeys.

It is important to note that four of these monkeys were running normal temperatures under ordinary room conditions. Two of these, monkeys 38 and 41, never showed definite hypothermia. The other two animals were tested on the twentieth and the forty-eighth day, respectively, at a time when they had recovered from severe hypothermia. These experiments, as well as those in the cold box, show the importance of such tests to disclose disturbances in heat regulation, which might otherwise be overlooked.

After removal from the warm box, the rectal temperature in five of the six monkeys with hypothalamic lesions continued to rise for a time before beginning to fall, while that of the normal monkeys began almost immediately to fall and fell more rapidly than in the first group of animals.

Hyperthermia.—Eight of the monkeys (in addition to monkey MC 36, which has not yet been killed) showed rather marked rises in temperature after operation. Most of them were operated on during June, when the room temperatures

were running rather high but, unfortunately, were not recorded. Two of the animals, monkeys MC 8 and MC 10, had been placed after the operation in an incubator set at from 84 to 86 F. In these eight animals the rectal temperature recovered within a few hours from the depression caused by the pentobarbital sodium and then rose rapidly above normal. The operations were finished around noon, and by 5 p. m. the rectal temperatures had reached 105.6 and 106.5 F., respectively, in two of the monkeys. Table 4 indicates the peak temperature and the time at which it was registered.

In most of these experiments the temperature fell to normal on the day after the operation, but in three it remained high on that day and did not fall to normal until the next day. All these animals were observed for some days after the operation, and the subsequent temperatures showed no marked deviations from normal. In three, however, the temperature fell to 98 or 99 F. on the third or fourth day. Unfortunately, none of the animals was subjected to low temperatures, and it is quite possible that had this been done they might have shown some loss in capacity to regulate against cold.

TABLE 4.—*Highest Temperature Reached by Hyperthermic Monkeys*

Monkey No.	Rectal Temperature, Degrees F.	Hours After Operation
MC6	106.0	21
MC7	105.8	9
MC8	104.5	4.5
MC10	106.5	5
MC12	105.0	9
MC13	105.6	5
MC14	105.0	9
MC34	104.4	5

LESIONS

A careful study of the lesions was made in serial sections stained alternately with the cresyl violet and the Weil stain. For each brain the extent and location of the lesions were indicated on a series of fifteen standard figures through the diencephalon of the rhesus monkey (reprinted from those in the article by Papez and Aronson [15]). Notes were made, showing for each brain the condition of each nucleus and of the chief fiber tracts—if they were damaged, to what extent and whether bilaterally or unilaterally. From these data, a chart was constructed which made it possible to see at a glance the condition of each structure in the entire series of brains. A study of this chart and of the drawings did not make it possible to locate the heat-regulating center in any particular nucleus or to show that a disturbance of regulation resulted from the interruption of any particular fiber tract. There was a funda-

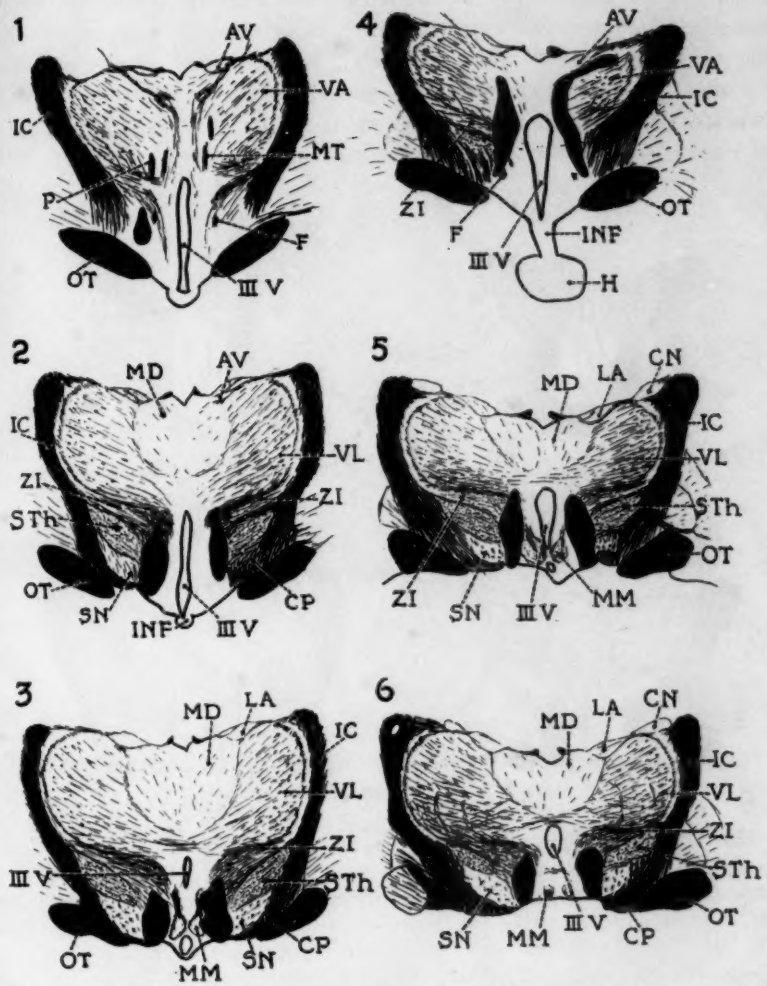
15. Papez, J. W., and Aronson, L. R.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: I. Ventral Thalamus, Arch. Neurol. & Psychiat. **32**:1 (July) 1934.

mental difference, however, in the location of the lesions in the monkeys in which hyperthermia developed and that of lesions in monkeys with hypothermia.

In all the monkeys which had shown hypothermia the lesions destroyed or seriously damaged bilaterally the region dorsal and lateral to the rostral end of the mamillary body, including that part of the nucleus of the ansa lenticularis which lies at this rostrocaudal level, as well as the intervening part of the nucleus hypothalamicus lateralis (figs. 1-6). The amount of damage to the hypothalamus rostral to the mamillary level and the dorsoventral level of the rostral part of the lesions varied greatly. In all but four animals the lesions extended backward as far as the caudal border of the mamillary bodies, and in two of the four the mamillary nuclei showed a marked increase in glia nuclei, throughout their extent. The lesions were situated chiefly in the lateral portion of the hypothalamus, and in most cases the walls of the ventricle escaped serious injury. The posterior hypothalamic nucleus was destroyed bilaterally in three animals, seriously damaged bilaterally in one and slightly damaged bilaterally in the others. The medial mamillary nucleus was completely destroyed bilaterally in two monkeys, seriously damaged bilaterally in six and slightly damaged bilaterally in the remaining five. The lateral mamillary nucleus was destroyed bilaterally in six animals, seriously damaged bilaterally in three and slightly damaged bilaterally in four. The nucleus intercalatus was destroyed bilaterally in nine animals, seriously damaged bilaterally in three and slightly involved bilaterally in two. The supramamillary commissure was completely interrupted in eight instances, incompletely interrupted in three and undamaged in two.

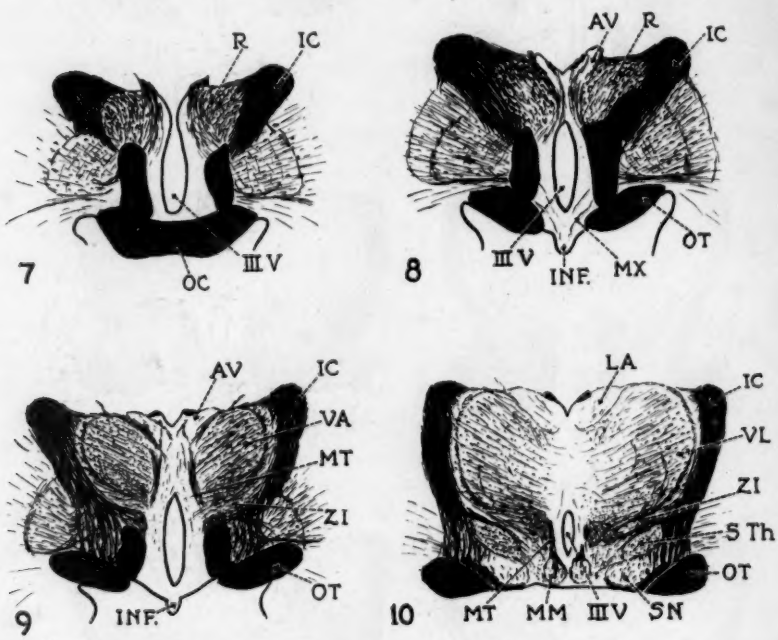
While it is not possible to fix on the particular structure bilateral destruction of which causes loss of the capacity to keep the body temperature up to the normal level, the results indicate that it probably lies dorsolateral to the rostral part of the mamillary bodies. Control experiments necessary to exclude the possibility that medially placed lesions might produce the same results, however, have not been made. Our results show clearly that any of the nuclei lying rostral to the mamillary bodies may be intact in an animal showing hypothermia. Of the thirteen animals, the filiform nucleus was intact bilaterally in twelve, the supraoptic nucleus in all, the ovoid nucleus in all, and the anterior hypothalamic nucleus in ten. The ventromedial hypothalamic nucleus was intact in four animals and only slightly damaged in seven; the nuclei tuberis laterales were intact in six and damaged only slightly in five. From this it is evident that none of the nuclei just mentioned plays an important part in guarding the body against abnormal drops in temperature. Since, as will soon be evident, these rostromedially placed nuclei

were intact in many of the monkeys in which hyperthermia developed after operation, it would not be unreasonable to conclude that they are not concerned with temperature regulation. This conclusion, however, needs to be checked by the study of animals with medially placed lesions.



Figs. 1-6.—Figures *1*, *2* and *3* represent frontal sections through the diencephalon of monkey MC 40, and figures *4*, *5* and *6*, similar sections from the brain of monkey MC 20. Lesions are indicated in solid black. In these drawings *AV* indicates the nucleus anteroventralis; *CN*, the caudate nucleus; *CP*, the cerebral peduncle; *F*, the fornix; *H*, the hypophysis; *IC*, the internal capsule; *INF*, the infundibulum; *LA*, the nucleus lateralis pars anterior; *MD*, the nucleus medialis dorsalis; *MM*, the nucleus mamillaris medialis; *MT*, the mamillothalamic tract; *OT*, the optic tract; *P*, the scar caused by puncture with the electrode; *SN*, the substantia nigra; *STh*, the nucleus subthalamicus; *VA*, the nucleus ventralis pars anterior; *VL*, the nucleus ventralis pars lateralis; *ZI*, the zona incerta, and *III V*, the third ventricle.

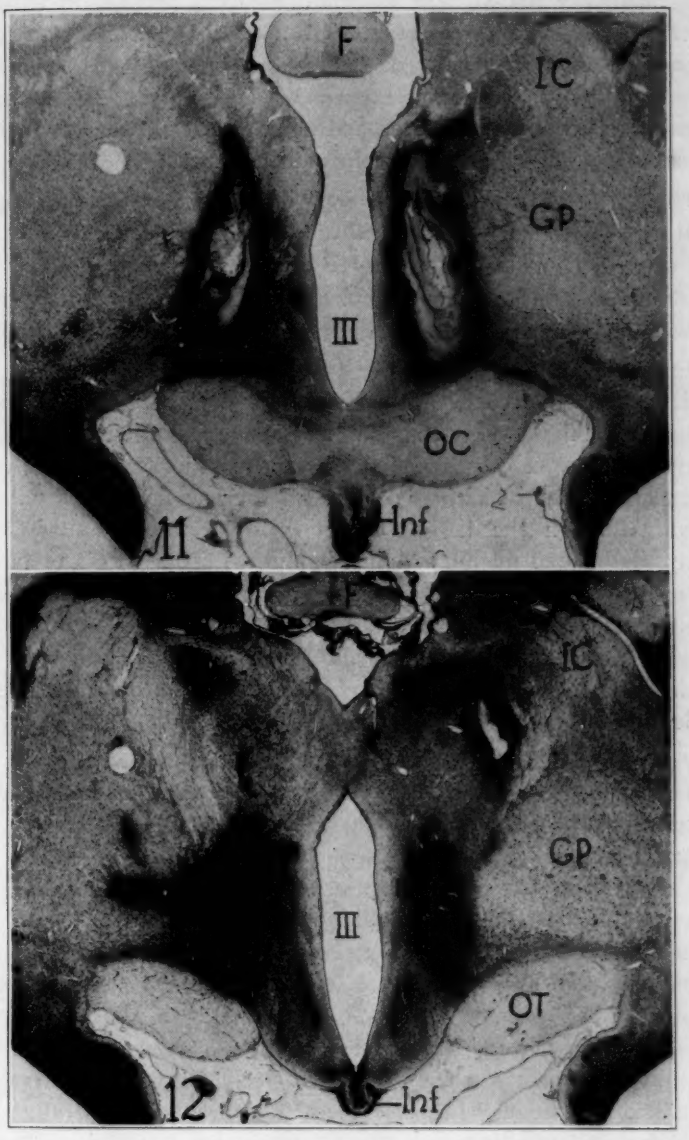
Figures 1 to 3 and 4 to 6 show the extent of the actual lesions in monkeys MC 40 and MC 20, respectively. In monkey MC 20 the lesions, as indicated in the figures, do not represent all the damage, for the nuclei situated between the lesions and around the ventricle showed a great deal of degeneration. The nerve cells were decreased in number, and the glia nuclei were increased. Similar changes were observed in the medial group of thalamic nuclei, including the nucleus medialis dorsalis. Nuclear changes of this general type and location were seen in many of the other monkeys. In monkey MC 40 the mamillary group of nuclei, situated between the lesions shown in figure 3, were rather



Figs. 7-10.—Drawings representing frontal sections through the diencephalon of monkey MC 13. Lesions are shown in solid black. In these drawings *AV* indicates the nucleus anteroventralis; *IC*, the internal capsule; *INF*, the infundibulum; *LA*, the nucleus lateralis pars anterior; *MM*, the nucleus mamillaris medialis; *MT*, the mamillothalamic tract; *MX*, Meynert's commissure; *OC*, the optic chiasm; *OT*, the optic tract; *R*, the nucleus reticularis; *SN*, the substantia nigra; *STh*, the nucleus subthalamicus; *VA*, the nucleus ventralis pars anterior; *VL*, the nucleus ventralis pars lateralis; *ZI*, the zona incerta, and *III V*, the third ventricle.

severely damaged, but rostral to this level there was little injury outside the actual lesions. The thalamus was intact except for the scars left by the punctures made when the electrode was inserted (*P*, fig. 1).

The location and extent of the lesions in monkey MC 13, in which the temperature reached 105.6 F. five hours after the operation, are



Figs. 11 and 12.—Photomicrographs (cresyl violet stain) representing frontal sections of the diencephalon and adjacent portions of the corpus striatum of monkey MC 12. The first section passes through the caudal border of the optic chiasm, and the second, through the caudal border of the infundibulum. The dark areas with or without light centers indicate the lesions. In these photographs *F* indicates the fornix; *GP*, the globus pallidus; *IC*, the internal capsule; *Inf*, the infundibulum; *OC*, the optic chiasm; *OT*, the optic tract, and *III*, the third ventricle.

shown in figures 7 to 9. Figure 10 shows the absence of any damage in the mamillary region. The lesions in monkey MC 12, in which the temperature reached 105 F. nine hours after the operation, are shown in figures 11 and 12. The dark stain is due to the gliosis surrounding the necrotic center. The section represented in figure 12 passes through the caudal border of the lesions and no cavity is shown except in the part near the internal capsule on the right side.

It will be seen that in both these monkeys the lesions involved the lateral part of the hypothalamus above the optic chiasm, extending backward over the optic tract to the level of the posterior border of the infundibulum or a little beyond, but not reaching the mamillary region. The walls and floor of the third ventricle were intact. In both monkeys the lesions impinged on the medial part of the globus pallidus.

All eight of the monkeys in which the temperature rose above normal during the first twenty-four hours after the operation were observed to have had lesions which were restricted to the rostral part of the hypothalamus, i. e., which did not extend back as far as the mamillary bodies. Although the lesions never involved the mamillary nuclei directly, the medial mamillary nucleus showed some gliosis unilaterally in three animals, and the lateral mamillary nucleus, unilaterally in three and bilaterally in two. The posterior hypothalamic nucleus was slightly damaged bilaterally in two animals. On the whole, however, these caudally located nuclei were relatively intact, as were the nucleus of the ansa lenticularis and the lateral hypothalamic nucleus at the level of the mamillary bodies.

In seven of the eight monkeys with hyperthermia, the lesions involved the rostral part of the lateral hypothalamic nucleus and the region around the fornix bilaterally. In one animal this region was involved unilaterally. The fornix was completely severed bilaterally by the lesion in six monkeys, completely on one side and incompletely on the other in one and completely unilaterally in the remaining animal. The anterior hypothalamic nucleus was intact bilaterally in five instances, and the ventromedial hypothalamic nucleus, bilaterally in two. When these nuclei were injured, the damage was slight or unilateral, except that the ventromedial hypothalamic nucleus was extensively damaged bilaterally in three animals. The nuclei tuberis laterales were intact bilaterally in two animals and unilaterally in two others. In no case were they completely destroyed. The filiform nucleus (nucleus hypothalamicus magnocellularis) and the supra-optic and ovoid nuclei were either intact or only slightly damaged. In the animal in which the lesions involved the lateral hypothalamic area and the region around the fornix on one side only, the walls of the suprachiasmatic portion of the third ventricle

were destroyed; and in one other animal the wall was damaged in the dorsolateral angle of the ventricle, dorsal to the filiform nucleus. But in all others the ependyma and the adjacent layer of the central gray matter were everywhere intact. In none of the eight animals did the lesions involve the floor of the ventricle behind the chiasm.

Damage to the thalamus can be excluded as a cause of disturbances in temperature regulation, for in this series the extent and location of such damage have varied widely but no relationship between such deviations and variations in thermostasis could be detected. Moreover, in another series of experiments we had monkeys which regulated their temperature normally with extensive lesions confined to the thalamus, chiefly in the medial group of thalamic nuclei in some animals and entirely in the lateral group in others.

Three of the eight monkeys which were able to maintain normal temperatures under ordinary room conditions had lesions similar to those showing hypothermia. Two of these three animals had subnormal temperatures when placed in a cool room, and the third was not tested in this way. In four monkeys the lesions did not reach as far ventrally as the fornix or the dorsal surface of the mamillary nuclei, and thus did not involve the regions destroyed in the monkeys with disturbed heat regulation. In one other animal the lesions were placed medially in the rostral part of the hypothalamus, destroying bilaterally the filiform, ovoid, anterior hypothalamic and ventromedial hypothalamic nuclei, as well as the walls of the rostral part of the third ventricle.

From all these observations it becomes clear that postoperative hyperthermia develops in the monkey when bilateral lesions are made in the lateral part of the rostral portion of the hypothalamus, i. e., in the region around the fornix rostral to the mamillary bodies. Hypothermia develops when the bilateral lesions are situated dorsolateral to the rostral part of the mamillary bodies. Tests in the cold room need to be made on monkeys with hyperthermia, since cats with rostrally placed hypothalamic lesions showed impaired regulation against heat, without any impairment of the capacity to resist cold (Teague and Ranson [16]). The more caudally placed lesions cause true poikilothermia. Five monkeys with impaired defense against cold (in two of which subnormal temperatures developed only when placed in a cool room) all failed to react properly when placed in the hot box.

COMMENT

The anatomic observations in Alpers' two cases of hyperthermia and in the case of hypothermia reported by Davison and Selby agree

16. Teague, R. S., and Ranson, S. W.: The Rôle of the Anterior Hypothalamus in Temperature Regulation, Am. J. Physiol. **117**:562, 1936.

perfectly with our observations on the monkey so far as the rostrocaudal levels of the lesions are concerned. If only the rostral part of the hypothalamus is damaged and the lesions do not reach back to the mamillary bodies, hyperthermia is likely to result. This is also in keeping with the observations of Teague and Ranson [16] that in the cat such rostrally placed lesions greatly diminish the animal's capacity to regulate against heat without impairing its capacity to maintain a normal temperature in a cold room. If the lesions in the monkeys involved bilaterally the region dorsolateral to the mamillary bodies, hypothermia resulted. This is in keeping with the observations in the case of Davison and Selby.

Davison and Selby attributed too much importance to the destruction of the nuclei tuberis laterales, since in the thirteen monkeys with hypothermia in our series these nuclei were intact bilaterally in six and only slightly damaged in five. The conclusions of Frazier, Alpers and Lewy that destruction of the anterior hypothalamic nucleus causes complete loss of temperature control, so that the animal's temperature falls below normal, is in diametrical opposition to the observations of Alpers that lesions in this same region cause hyperthermia in man. It is also contrary to the observations of Teague and Ranson on the cat and to our results on the monkey. Moreover, in their cat 13/10, which they present as typical of their best results, the lesion, as illustrated in figure 2 B, is large. The damaged area extends in a broad band from the caudal border of the optic chiasm diagonally dorsad and caudad, to the habenular nuclei. The width of this band was more than one-sixth the width of the entire brain, and its length was two fifths of the distance from the optic chiasm to the dorsal surface of the cerebral hemisphere.

In the two cases of hyperthermia in man, the lesions were described by Alpers as confined to structures near the wall of the third ventricle, while of the eight hyperthermic monkeys in our series the wall of the third ventricle was involved in only two, the lesions being situated farther laterad, in the neighborhood of the fornix. Obviously, the functional impairment must have extended farther mediad than the lesions would indicate in our monkeys, or farther laterad in Alpers' cases. Further work will be required to determine whether the center concerned is situated medially or laterally. It is, however, gratifying to have the rostrocaudal levels of the lesions in Alpers' cases, the cats in the series of Teague and Ranson and the hyperthermic monkeys in our series in such close agreement.

The monkeys with hyperthermia quickly regained the ability to keep the body temperature down to normal, and in the animals with hypothermia a certain degree of recovery occurred with the lapse of days or weeks. From the data at hand, it is not possible to say what factors are responsible for such recovery. It might be assumed that the heat-

regulating center or centers had not been completely destroyed by the lesions or that subsidiary centers took over the function (Keller [9] and Thauer [12]).

SUMMARY

The temperature of the normal monkey varies considerably and is raised quickly by struggling. The rectal temperature of the resting monkey may range from 100 to 101.5 F. Room temperatures of from 102 to 104 F. cause the rectal temperature to rise quickly to dangerous heights.

Lesions in the hypothalamus may cause either transient hyperthermia or more prolonged hypothermia.

In animals with hypothermia the lesions were observed to have extended backward to the level of the mamillary nuclei, while in those with hyperthermia the lesions were confined to the rostral part of the hypothalamus. The lesions in these animals were placed bilaterally in the lateral part of the hypothalamus and seldom involved the walls of the third ventricle, but the possibility that medially placed lesions might produce the same results has not been excluded.

Recovery from hyperthermia usually occurred within twenty-four hours. Hypothermia lasted many days but disappeared as a rule within a month. Even after the hypothermic monkeys had recovered sufficiently to maintain normal body temperatures under ordinary room conditions, they were still unable to compensate normally for high or low room temperatures.

DISCUSSION

DR. PERCIVAL BAILEY: Dr. Ranson suggests that the anterior part of the hypothalamus is concerned in maintaining the temperature against heat, and the posterior part, against cold. The location of the lesions seems to be such that they might interrupt the tracts from the nuclei in the anterior part; that might interfere with both parts of the hypothalamus. I wonder if Dr. Ranson has any remarks to make about this point.

DR. ISIDORE FINKELMAN: Would it make any difference whether the lesions were placed laterally or medially?

DR. PAUL C. BUCY: I wish to ask Dr. Ranson whether the paraventricular nuclei take any part in this thermal regulation. In the sections, particularly those from the monkey, it appears that these nuclei, lying lateral to the third ventricle, have undoubtedly been destroyed.

DR. S. W. RANSON: Dr. Bailey's point about the interruption of descending paths by the posterior lesions is well taken. The animals with the lesions far back had loss of regulation both against heat and against cold, and we interpreted this as meaning that the tracts leading backward from the center for regulation against heat in the anterior part were interrupted, along with the damage to the center for regulation against cold in the posterior part.

The question raised by Dr. Finkelman as to medial and lateral lesions requires careful consideration. I did not go into that tonight, but Dr. Alpers maintains that in his patients with hyperthermia the lesions were medially placed. Certainly, in the hyperthermic monkeys in our series the lesions were well lateral, and the

wall of the third ventricle was not damaged. But in the cats with anterior lesions in our series the damage was placed medially in the floor of the third ventricle and produced loss of regulation against heat. This agrees well with Alpers' observations. Lesions placed laterally in the caudal portion of the hypothalamus cause loss of ability to regulate against cold, but we have not yet made any medial lesions in the caudal part. I am willing to leave open for the moment the question of medial and lateral location but am convinced that there is a distinct difference between the anterior and the posterior part.

In answer to Dr. Bucy's question I can say only that it has not been possible to show that any particular nucleus is responsible for regulation of temperature.

ANTEROLATERAL CHORDOTOMY FOR INTRACTABLE PAIN OF TABES DORSALIS

EDGAR A. KAHN, M.D.
AND
BURTON F. BARNEY, M.D.
ANN ARBOR, MICH.

Control of the gastric crises and lightning pains of tabes dorsalis has long presented a difficult problem. The operation of anterolateral chordotomy, first performed by Martin at the instigation of Spiller [1] and extended in scope by the work of Foerster,[2] should, when perfectly performed, relieve all pain below the clavicles. Chordotomy has now been performed on twelve patients in the clinic of Dr. Max M. Peet for various types of tabetic pain. Though the results are far from perfect, we believe that enough has been accomplished in the way of relief of intractable pain to warrant their publication.

The following history of severe, long-standing gastric crises presents a typical problem, with its ultimate satisfactory solution.

REPORT OF A CASE

W. S., a clerk aged 34, was admitted to the University Hospital on June 15, 1927, complaining of almost daily attacks of severe epigastric pain, associated with vomiting. This had been noted first three years previously. Two years after the onset of symptoms he was seen at the Mayo Clinic, where a diagnosis of tabes dorsalis with gastric crises was made. The Wassermann reaction of the spinal fluid at that time was four plus. Considerable antisyphilitic therapy was administered, without affecting the crises.

On entrance to the University Hospital, a course of malarial therapy was given, without improvement. In September 1928 anterolateral chordotomy was performed to a depth of 3 mm. bilaterally, at about the fifth dorsal segment. The level of loss of pain and temperature sensation was approximately at the umbilicus. The attacks continued.

From the Departments of Surgery and Dermatology and Syphilology, the University of Michigan Medical School.

1. Spiller, W. G., and Martin, E.: The Treatment of Persistent Pain of Organic Origin in the Lower Part of the Body by Division of the Anterolateral Column of the Spinal Cord, J. A. M. A. **58**:1389 (May 18) 1912.

2. (*a*) Foerster, O.: Ueber die Vorderseitenstrangdurchschneidung, Arch. f. Psychiat. **81**:707-717, 1927. (*b*) Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

In February 1929 the greater and lesser splanchnic nerves and part of the sympathetic trunk were sectioned bilaterally by Dr. Peet, again without relief of pain. Later, the rami to the eleventh and twelfth ganglia on both sides were divided, to no avail.

In February 1934 chordotomy was performed at about the eighth cervical segment, to a depth of 4 mm. bilaterally The analgesia extended (fig. 1) to just below the clavicles. There has never since been any epigastric pain or vomiting. The patient has been working daily in an automobile factory. There is difficulty in starting the urinary stream on arising in the morning, but during the remainder of the day the bladder functions normally.

Comment.—After the first chordotomy the analgesia extended only to the umbilicus. Since the pain during the gastric crises was referred high up on the epigastrium, relief scarcely could have been expected until the analgesia extended

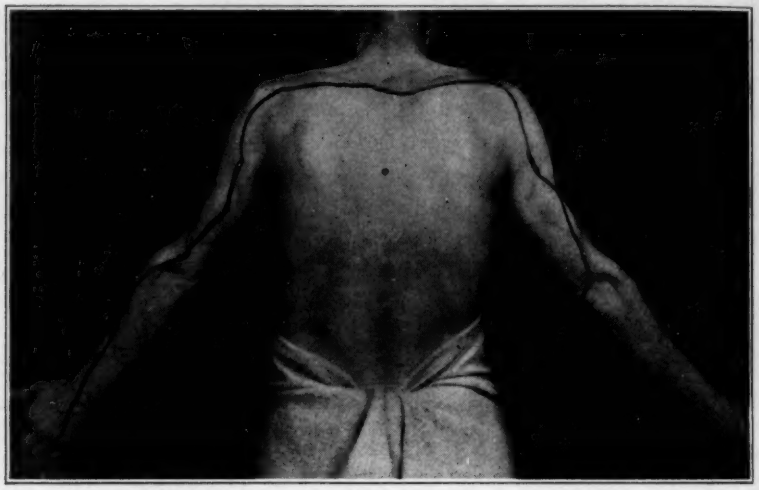


Fig. 1.—Photograph of W. S., showing analgesia to the first dorsal dermatome on the right and to the eighth cervical dermatome on the left. The old dorsal incision and the more recent cervical incision are just visible.

to above the radiation of the pain. At the second chordotomy, a deeper incision into the anterolateral tracts at a higher segment of the cord resulted in sufficiently high analgesia for complete relief of the gastric crises.

HISTORICAL SKETCH

It was Foerster [2] who, through exact work on the anatomic and physiologic features of the anterolateral columns, first demonstrated that pain and temperature fibers, entering the posterior roots, cross over immediately on synapsing in the posterior horn or, at most, ascend one segment before crossing over to pass upward in the spinothalamic tract. Thus, by means of an incision into the anterolateral tracts (fig. 2), from 4 to 4.5 mm. in depth, at the eighth cervical segment,

where one ordinarily performs chordotomy for any pain below the clavicles, analgesia is obtained to the first dorsal dermatome.

Chordotomy for pain attributable to tabes dorsalis was resorted to first by Tietze, at Foerster's [2] suggestion. Foerster himself has since performed the operation eleven times for the same condition. In seven of the cases the results were entirely satisfactory.

TECHNIC

In a previous communication by one of us (E. A. K.) reporting seventy-eight cases of chordotomy performed by Drs. Peet, S. S. Allen and Kahn,[3] for various conditions, the following statement was made:

"A pointed knife with bone wax, marking off from 3 to 5 mm., is inserted at the line of dentate attachment and emerges through an anterior nerve root."

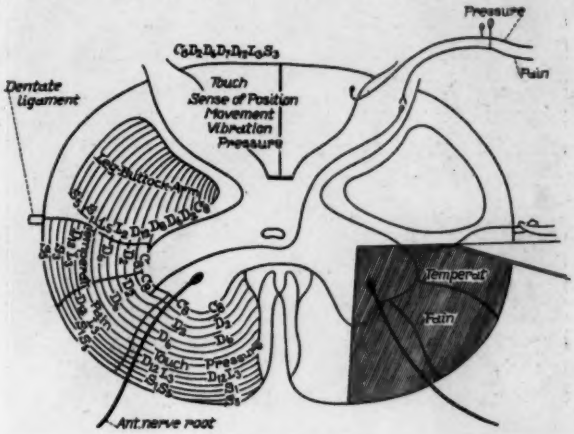


Fig. 2.—Schematic drawing (after Foerster [2]) of the eighth cervical segment, showing a pointed knife blade entering the spinothalamic tract just anterior to the dentate ligament and emerging beyond the anterior nerve root.

We now feel strongly that the incision should be carried farther anteriorly; that is, at least 2 mm. beyond the emergence of the anterior nerve root (fig. 2). Though the patients are more likely to complain temporarily of numbness in the legs, our results during the three years since this publication have improved considerably. It was stated also that local anesthesia was the anesthetic of choice, in order that the level of analgesia might be tested during operation. We have found on occasion, however, that even on the day following operation the level has fallen, the deeper fibers apparently having been traumatized temporarily. We now believe that tribromethanol anesthesia should be used. The operation can be performed more accurately and safely on an unconscious patient than on one struggling from the pain caused by traction on roots of the posterior nerves during the rotation of the cord which is necessary for proper section of the tracts.

3. Kahn, E. A.: Anterolateral Chordotomy for Intractable Pain, J. A. M. A. **100**:1925-1928 (June 17) 1933.

Complications.—In all but one of our cases in which bilateral chordotomy was performed, there was disturbance of the bladder, in the nature of retention. This eventually has disappeared entirely in more than half of the cases. The continuing disturbance has been in the nature of incontinence, either true or paradoxical. It must be remembered that many tabetic patients have bladder symptoms before operation.

Recurrence of pain may take place early from an insufficiently high sensory level, as occurred in one of our cases, or at a later date with a fall in sensory level, as took place in two of Foerster's cases and in one of our own. Reoperation is then necessary.

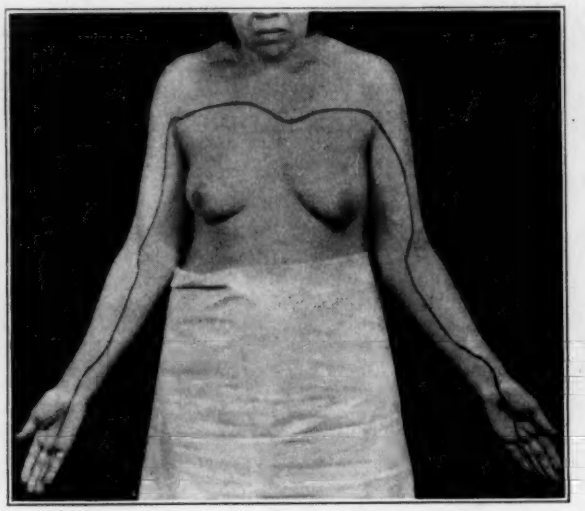


Fig. 3.—Photograph of patient H. P. showing analgesia to the eighth cervical dermatome on both sides.

It might be expected that in the tabetic patient in whom there is already some involvement of the posterior column, section of the anterolateral columns would increase the ataxia markedly. We have, surprisingly, found no evidence of this. In only one instance was walking disturbed by the operation. In this case the right pyramidal tract was accidentally injured during laminectomy, prior to section of the anterolateral tract. This injury, which occurred under local anesthesia, was recognized at the moment it happened. In none of our other cases was there damage to the pyramidal tracts.

The patient suffering with gastric crises is ordinarily in a poor state of nutrition. The tabetic patient is, moreover, prone to trophic disturbances, so that when analgesia is produced by operation, pressure

Name	Sex	Age on Admission, Years	Date of Infection	Treatment Before Neurologic Symptoms	Onset of Neurologic Symptoms	Kahn Reaction of Spinal Fluid and Diagnosis	Subsequent Treatment*	Chordotomy with Immediate Results	Subsequent Condition	Summary
P. V.	M	47	1901	None	1915: Gastric crises	++++ Tabo-paresis	I.V., I.M. and I.D.	3/18/26: Complete relief of pain	Suicide 6/26/26	Pain relieved; paresis may have been cause of suicide
G. R.	M	56	1893	None	1908: Pains in legs and ataxia	++++ Tabes	I.V., I.M. and potassium iodide	11/2/26: Complete relief of pain	Died—cause unknown	Satisfactory result, as patient had relief of pain as long as he was followed
C. R.	M	51	1895	Local	1915: Pains in legs and ataxia	— Tabes	None recorded	3/21/28: Unilateral relief of all pain	Not traced; no pain when seen 5 years ago	Satisfactory result
W. S. (fig. 1)	M	34	Not known	None	1925: Gastric crises	++++ Tabes	I.V., I.M., I.D. and malaria	9/11/28: No relief; 2/4/29 bilateral splanchnic section, no relief; 3/5/29 section of 11th and 12th thoracic rami, no relief; 2/2/34 complete relief	Complete relief of gastric crises; this case is detailed in body of article	Satisfactory result; slight residual bladder symptoms; patient working daily
J. W.	M	51	Not known	None	1913: Tabetic pains in legs; gastric crises	++++ Tabes	I.V., I.M. and I.D.	1/19/33: Relief of pain; one pyramidal tract damaged; incontinence and paralysis of one leg	Relief of pain; motor power returning; mild vesical atony	Technic imperfect, but result was satisfactory to patient
W. E.	M	40	1921	Inadequate	1928: Gastric crises	++++ Tabes	I.V., I.M., I.D. and malaria	2/4/32: Relief of all pain; temporary cord bladder	Complete relief	Satisfactory result; patient working daily
D. K.	F	19	Not known	None	7/5/28: Tabetic pains in abdomen	++++ Tabes	1928: Appendectomy; cholecystectomy; I.V., I.M. and I.D.	3/2/33: Return of pain; 5/2/33 return of pain; 8/3/33 return of pain; 8/25/33 dorsal symptoms; return of pain; 9/9/33 pseudo-operation, temporary relief from pain	Return of pain; suicide	At a short interval after each operation, the sensory level obtained disappeared. We are at a loss to explain this; hysteria, no doubt, played a part
R. C.	M	63	Not known	None	1919: Tabetic pains in legs	Test not done; tabes	Unknown	6/28/34: Unilateral relief of all pain	Complete relief	Satisfactory result
E. S.	M	58	Not known	None	1914: Tabetic pains in legs and gastric crises	++++ Tabes	I.V., I.M. and malaria	9/7/34: Relief; mild pain	Relief	Patient still complains of mild pain; local doctor states patient has received considerable benefit
H. S.	M	37	1925	Good	1930: Gastric crises	++++ Tabes	I.V., I.M., I.D. and malaria	6/19/35: Relief of all pain	Complete relief	Satisfactory result
L. S.	M	55	1909	None	1919: Tabetic pains in legs; gastric crises	Tabes	I.V., I.D. and I.M.	9/17/35: Death 10th day after operation	Death 10th day after operation	This patient was an extremely poor perative risk; death due to inanition; relief of pain at time of death
H. P. (fig. 3)	F	32	Not known	None	1930: Tabetic pains in legs; gastric crises	— Tabes	I.V. and I.M.	3/9/36: Relief of all pain	Complete relief	At the time of writing, one month after operation, the patient had had no return of pain

* In the table, I.V., I.M. and I.D. represent intravenous, intramuscular and intradermal injections.

sores must be carefully guarded against. One other complication should be mentioned. After section of the anterolateral tracts, erection and ejaculation may still take place, but voluptuous sensation is lost, since it is carried in these tracts. Most tabetic persons are impotent by the time they come to operation, so that this is a comparatively unimportant factor.

COMMENT

It is not our purpose in this paper to discuss the therapeutic prevention [4] of tabes in syphilitic patients, although all but one patient in this series had had little or no therapy before the onset of neurologic symptoms. It is evident, however, that in all cases presented, late treatment in the form of the arsphenamines, heavy metals and potassium iodide and even malaria therapy did little for the patient's symptoms.

Chordotomy up to this time has been a procedure of last resort, carried out when the general condition of the patient was poor, which thus increased the operative risk. In spite of this, only one postoperative death resulted. This occurred on the tenth day, in a debilitated patient whose prognosis for life, even if no operation had been performed, was none too good.

SUMMARY

It is realized that in certain cases malaria and fever therapy may be of value. The contraindications to fever therapy are, however, numerous and need not be considered here. What we wish to stress is that when standard methods of treatment fail for the intractable pain of tabes dorsalis, the comparatively neglected procedure of anterolateral chordotomy should be tried. In at least eight of the twelve cases presented, the pain of tabetic origin had been relieved entirely when the patient last reported.

Brief histories in the twelve cases mentioned, together with treatment and the results of operation, are recorded in the accompanying table.

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4. Wile, U. J.; Poth, D. O., and Barney, B. F.: Dementia Paralytica and Tabes: Study with Reference to Precocious Development, J. A. M. A. **105**:1329-1333 (Oct. 26) 1935.

THE PSYCHOPATHOLOGY OF PICK'S DISEASE

KURT GOLDSTEIN, M.D.
AND
SIEGFRIED E. KATZ,† M.D.
NEW YORK

The fact that atrophy in Pick's disease involves especially the frontal lobes should induce one to look for symptoms which are known to be characteristic of lesions of the frontal lobe. In the description of the symptomatology of Pick's disease there is some evidence which points to a functional disturbance of the frontal lobes. Formerly, however, it was not possible to base the diagnosis on psychologic disturbances, as the mental changes which are characteristic of lesions of the frontal lobe had not yet been recognized. Today, knowledge has advanced greatly, and it appears justifiable to make a diagnosis of a lesion of the frontal lobes on the basis of mental changes. The case to be reported may demonstrate that it is possible to diagnose Pick's disease on psychologic criteria alone. However, it must be stated that the diagnosis is not certain until postmortem confirmation is obtained. We do not doubt the diagnosis because the encephalographic picture is typical of atrophy of the cerebral cortex, especially of the frontal lobes. These facts amply support our position. Naturally, further examinations are needed to verify this standpoint. The great rarity of Pick's disease makes it impossible for a single author to be absolutely certain on this point.

This article is meant to help in this direction, particularly by suggesting further inquiry and examination of patients afflicted with Pick's disease in the manner herein outlined. The mental picture typical of a lesion of a frontal lobe is to be expected at the onset of the disease, when the personality has not yet changed to such a degree that good cooperation and an exact examination are impossible (a condition common in such cases). Our case was well adapted for this purpose. For those in which the process is more advanced it will be important in the diagnosis if one can demonstrate that the severe mental deterioration has developed from a behavior picture characteristic of lesions of the frontal lobe and that many particular phases of this behavior can still be found.

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† Dr. Katz died on Dec. 14, 1935.

From the New York State Psychiatric Institute and Hospital.

Dr. Clarence O. Cheney, director of the Psychiatric Institute, and the Rockefeller Foundation gave me the opportunity of working at the institute during 1935.

REPORT OF A CASE

History.—Martha O., aged 56, was born in Sweden. Her early development was normal. There had been no neurotic manifestations; she was always jolly, sociable and active. She had average intelligence. She menstruated first at 15 or 16 years. At the age of 20 she became a dressmaker, and she was clever at this work. In 1914, at the age of 32, she came to the United States. She married in 1922. She had much difficulty with her husband; he lost his money and borrowed sums which he could not repay. He became a periodic drinker and would come home intoxicated. She continued to work. Their home was pleasant, and, aside from the unfortunate incidents with her husband, she was happy. Life was a continual strain, however, because of financial uncertainty. She was always patient with her husband and with her own difficulties. The blood of the husband at one time gave a positive Wassermann reaction.

The family history showed nothing unusual; there was no abiotrophic neurologic condition. No similar disease had occurred in the family. Three brothers and two sisters were normal. The patient was the second child. Before the onset of the present disease there had been no attacks of mental disorder.

First Symptoms of the Psychiatric Disorder.—About a year and a half before the examination the husband noted that the patient frequently burned food when cooking because she forgot that it was on the stove. She gradually lost interest in working. She would sit at home and read the weekly periodicals, perusing the same stories over and over again, showing the same interest in them and not realizing that she had read them before. Shortly afterward a brother died; she imagined frequently that she saw him. She would run out into the street, even when undressed, to talk to him. She stated that she knew he was dead but that it must be he. She tired easily and would lie down often during the day. Her appetite remained good. She occasionally complained of mild headache; she felt somewhat sad at first. The content of her thoughts was all "mixed up." During the night she had to go to the toilet many times. No evidence of apraxia or aphasia was ever noted by the husband. In physical appearance, whereas she had been neat she became "sloppy." If she was aroused or if any criticism was made of her appearance, she became angry. She recognized her husband, her sister and her dog, but she was confused about the identity of other persons. Her thoughts were bizarre. She told of long conversations with her brother shortly before he died. This was impossible, because he could not speak at that time. After his death she had imaginary conversations with him. She would talk of seeing the "funniest cat" across the street; it had legs all over its body, with one claw on each leg; she stated that it loved to sit in her lap and suggested that in locomotion it would roll along. She imagined that she saw a friend going across the street to give a message.

She was taken to the Neurological Institute, where she stated that her brother came into the ward and made a "rumpus." She believed that a cat came along too and died and lay behind her bed. She cried frequently because she fancied seeing her brother in the street and going away hungry. She would frequently sit and sing as she read, something which she had never done before. Gradually she became happier, rather euphoric. She seemed not to be in the least self-conscious. At night she was restless.

Mental Status on Admission.—In the ward the patient usually sat on a bench in a corner of the hall with her arms folded and a smile on her face, attentive to events taking place. When asked to help with the work in the ward she usually said: "I'll be all right" and did nothing further. In matters of general

routine she was usually cooperative. During interviews she seemed restless and hyperactive. She smiled constantly and looked at the examiner in an attentive manner. She answered questions quickly. Her speech was somewhat flirtatious and precise. Her answers usually consisted of one sentence, and the content was usually an attempt to cover defects in memory. Her mood was constant, although a degree of irritability had been noted.

In the morning visitors were usually greeted by her with a smile. She then waited for further conversation. If none was forthcoming, there was no further production on her part and she did not seem disappointed. During interviews she usually had an expression of anxiety on her face and in her voice, waiting to see whether her answers would fit properly into the situation. She was happy, elated and somewhat euphoric. If asked how she felt, she would always answer: "I'm always nice." Even when discussing such events as the death of her brother, which was supposed to have been a considerable shock to her, she maintained her jovial manner. She sometimes had hallucinations, delusions and illusions. These were bizarre and centered chiefly about her brother. The most marked mental defect lay in the sensorium; there was a marked loss of memory. She was oriented to some degree as to place and person, but poorly as to time. She had little conception of her own age or of when she was born. She did not remember when she was married or when she came to the United States. She was unable to give the address at which she lived, adding that she lived with her four children, Alvin, Margaret, Bernard and Rita. These are the names of brothers and sisters. She did not know where she was one week before and said that she was "going home tonight." This answer was constant. When spoken to she would give the same response. She was able to do simple calculation, but when it became more complicated she failed completely. Her interpretation of the dog story was: "I read about the dog; he was nice to his master." There was definite evidence, as judged from her behavior in the ward and during interviews, that there was marked intellectual deterioration. She had little insight, and her judgment was exceedingly poor.

Physical Examination.—The patient was 167 cm. tall and weighed 89.3 Kg. The excessive fat had a diffuse distribution. The complexion was ruddy and the texture of the skin fine. The hair was gray. The heart was not enlarged, and the heart sounds were clear. The pulse was strong, but there was a tendency to bradycardia with a rate of 54 per minute. The volume of the heart beat was good. There was moderate arteriosclerosis, not incompatible with the age 56. The blood pressure was 142 systolic and 86 diastolic. The liver appeared normal. Gynecologic examination revealed no serious pathologic condition in the pelvis; however, a vaginal discharge suggested an infection with Trichomonas vaginalis. Ophthalmologic examination showed moderate arteriosclerosis, but the disks appeared normal. The pupils were equal and regular and reacted well to light and in accommodation. Fine vesicular twitchings were noted about the mouth; the function of the cranial nerves was normal. Coordination and strength were normal in the extremities; the reflexes were equal and active.

At the Neurological Institute a Babinski sign was obtained on one occasion on the left. This could not be verified later. Some inequality of the reflexes also was noted; this varied from examiner to examiner. On examination at the Psychiatric Institute, however, the reflexes were equal on the two sides. There was no aphasia or apraxia.

Examination of the blood revealed: red blood cells 4,630,000, white blood cells 6,200, hemoglobin content 87 per cent and color index 0.93; the cells were

normal morphologically. A differential count revealed: 61 per cent polymorphonuclears, 33 per cent lymphocytes, 4 per cent large mononuclears and 2 per cent eosinophils. The urine was cloudy and yellow, with an acid reaction; the specific gravity was 1.028; there was a faint trace of albumin, and sugar was absent. Microscopically the urine contained many crystals of uric acid, many crystals of calcium oxalate and a moderate number of leukocytes. The Wassermann reaction of the blood was negative. Chemical studies of the blood showed: urea nitrogen 14.5 mg., uric acid 2.7 mg. and sugar 94 mg. per hundred cubic centimeters. The basal metabolic rate was —14 per cent and 13 per cent on two different occasions. The spinal fluid contained 2 cells, and 25 mg. of protein per hundred cubic centimeters; the colloidal gold curve was 1110000000, and the Wassermann reaction was negative.

Roentgen Studies: Flat films of the skull showed no abnormality. In an encephalogram taken on Oct. 11, 1935, the lateral ventricles appeared slightly larger than normal, but symmetrical. A large amount of air was congregated over the frontal lobe, particularly in the polar region. The sulci were widened, and the gyri were narrowed, indicating a marked degree of atrophy in this region. Definite widening of the sulci was noted also in the temporoparietal region, but this was not as marked as in the frontal lobe; here a few scattered sulci were definitely enlarged.

Course.—Further observation gave the following picture: The patient in general is quiet and orderly; she adapts herself well to the environment of the clinic, complies with the tasks set before her and will speak with fellow patients and with nurses. She eats without help, taking small amounts of food. She dresses herself and is willing and ready to help in work in the ward, mostly knitting, which she does correctly. She welcomes the doctor as an old friend and is always cheerful and ready for conversation. Conventional movements of expression are not lacking; they seem even to be somewhat exaggerated. In conversation she is much interested in the point under discussion; the formal course of conversation, the rhythm and the structure of sentences are unchanged.

Contrary to these apparently normal performances, however, the general behavior is highly stereotyped. When alone in the ward she walks up and down. She welcomes with friendly gestures every person who comes into the room but does nothing and speaks to nobody spontaneously; she does not appear to desire or ask for anything. She begins nothing on her own account. When guided into the bathroom she will wash herself, but, according to nurses, she will never ask to wash herself or even perform the act on her own initiative. Similarly, she undresses in the evening when told, but never does so spontaneously; when tired she would lie down on her bed fully dressed. It always appears necessary literally to push her into action by a concrete situation. It would not be correct to say that she is inattentive and inactive, for, as mentioned earlier, she reacts to many and diverse objects and often may even appear diverted. More striking, however, is the fact that she often does not pay attention to a person who visits her in her usual surroundings, for example, the physician; when taken to his office, however, she welcomes him with a natural expression. Seeing her shifting from one subject to another without comprehending any one of them, sitting inactively for a long time or walking up and down without apparent aim, one might form the impression that she is incapable of executing a job demanding steadiness and concentration for any length of time. This assumption proves incorrect, however, from further observation. For example, when asked to lead the way quickly to

the workroom, she takes a complicated route promptly and naturally. When asked to write something, she takes the pencil and writes apparently with interest and certainly with energy and concentration.

COMMENT

These examples and other similar ones illustrate that all existing labels are unsuitable to describe the behavior of the patient in an unambiguous way. A more thorough examination, with set tasks, shows what performances the patient is unable to do and the kind which she can do well. We shall illustrate the behavior of the patient by a typical example selected from many protocols. Here, it is well to mention that no data have been omitted which might lead to a contrary interpretation from that presented here. Lack of space prevents presentation of all the protocols. The following example will illustrate the characteristic features of the patient's behavior.

After a short conversation she was asked what she had been doing during the day. She answered: "I am working." When asked where, she offered to lead the way to the workroom. (This room is situated on an upper floor of the hospital.) She went directly across the floor to the end of the ward, where there was a closed door, and glanced at the nurse, apparently desiring her to open the door and realizing that the door was locked. She opened the door with a key given to her, locked it from the outside, returned the key to the nurse, went straight to the elevator situated on the other side of the corridor, rang correctly and entered it on its arrival. On reaching the floor of the workroom she left the elevator at the direction of the operator, went directly to the door of the workroom and immediately took her place at the table. She then asked for her needlework from the supervisor of the workroom, prepared her material and started to knit. All this was done without the least hesitation and with vivacity. When asked at this point to put away the needlework and to accompany the physician, she became startled, seemed bewildered and was reluctant to do so. Great effort was needed to move her. Eventually, she arose and left, taking the correct route out and heading for the elevator. When stopped before she reached the elevator while still on the same floor, which is identical in structure with the floor on which her ward is located, and led into the corridor, she believed it was the floor on which her ward is located. She then walked through the corridor as if she were on the ward floor and turned to the right at the end of the corridor as though she were about to enter her sleeping room. She was surprised to find herself in a room unknown to her. When told that she was on the wrong floor she became perplexed and looked around but was unable to find the correct way to the ward. She not only was ignorant of where she was but did not know how to return to the ward.

This example illustrates that the patient is able to take a complicated path as would a normal person who knows his way. When she is interrupted in this task, which she is accustomed to do in a specific manner, she loses orientation in space. Thus, her behavior is determined by the concrete stimuli of the situation, and she performs well

as long as the stimulation is of this concrete nature. Her behavior in familiar surroundings will vary in correctness. She fails immediately when the task demands that she give an account to herself as to relations in space, the way from one place to another, etc. This may be deduced from the fact that she cannot describe the route, although she follows it correctly. For example, she will take the correct path from the one floor to the other but knows nothing about the situation of the floors or the relation of one floor to the other.

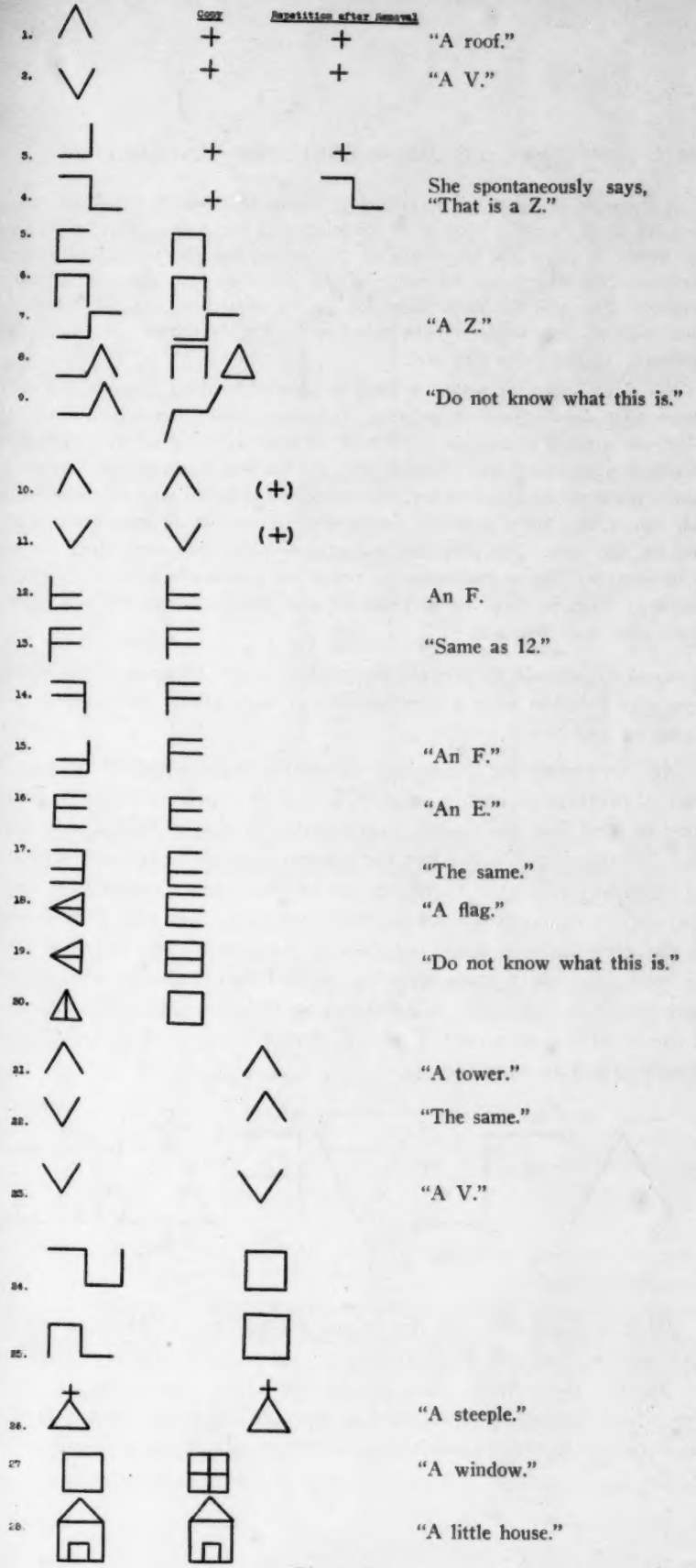
The example demonstrates also that stimuli which seem to contain a definite impulse affect the patient in an almost irresistible way. This became clear when, while on the wrong floor, she appeared to be driven by the appearance of the floor to go directly to the end of it. A similar illustration is as follows:

> The patient is well able to use her hands in manipulating familiar things. Occasionally, when she is holding her knitting materials in her hands, we ask her to show us her work. However, she fails to understand that her task is simply to show the work—rather, the sight of the knitting material seems to induce in her the idea that she must work with it.

This inability to demonstrate something or to show how it is done, the projection of her entire being into a situation in a compulsive way and the reaction to the passive prompting by a definite situation are a characteristic feature of the behavior which will be discussed more fully later.

The example given shows further that the failures are not due to lack of memory. The execution of these complicated tasks surely would not have been possible without good recollection of past experiences. It really was not determined only by the given stimuli in the actual environment. When it is necessary to proceed with the action of opening the door, the patient recalls well the process necessary for carrying out this purpose; she remembers the necessity for using a key and asks for the key. She even demands it before trying to see whether or not the door is locked, knowing that it is locked. Later, when standing before her place in the workroom she asks naturally for her knitting material. Memory images evidently arise in what appears to be a normal manner when they are needed for carrying out a definite action, but the capacity for memorization is poor when she is required by the situation to produce images voluntarily; for example, to give an account of the relations of the floors to one another. However, there seems to be no gross defect in involuntary memorization. In this respect memory seems to be little, if at all, affected. This also holds true for intention, interest, etc.

The same trends are found over and over again in various experiments. We shall report some results which were obtained in different spheres of performance.



"A roof."

"A V."

She spontaneously says, "That is a Z."

"A Z."

"Do not know what this is."

An F.

"Same as 12."

"An F."

"An E."

"The same."

"A flag."

"Do not know what this is."

"A tower."

"The same."

"A V."

"A steeple."

"A window."

"A little house."

Figure 1

1. *Behavior to Space.*—The patient is aware of being in a hospital, but she does not know its name. She gives the address of her home. She does not know the names of either the physicians or the nurses, but she recognizes their professions. She does know the name of the physician who saw her first at the hospital. She uses the same name for all the physicians, but she differentiates them well as individuals. When asked as to the difference, she says quickly, smiling: "Oh, he looks very nice."

We place before the patient a small wooden stick, about 3 inches (7.5 cm.) in length, in a definite position, pointing, let us say, from lower left to upper right. First, she is asked to copy the position of the stick with another stick given to her. This task is performed well. Second, after she has been asked to note well the position of the stick placed before her, this stimulus is removed after exposure for one-half minute, and she is given the second stick to place in the same position as the one she had seen. She does this correctly at times, but more often she places it incorrectly. She is then asked to repeat the combinations of sticks shown in figure 1: first, to copy the arrangement and then to repeat the task after the sticks have been removed.

It is impossible to prevent the patient from bringing the given pattern into relation with a concrete object and calling the picture by the name of this object.

In reviewing the foregoing facts one must ask: Why does the patient perform so well in some tasks and so poorly in others? First, it may be said that she usually succeeds in copying patterns lying before her. Errors occur only when the pattern is removed and she is required to reproduce it later. However, she is observed to perform in various ways when confronted with different patterns. She performs correctly if the given pattern appears to her as a concrete object that is known to her. She has a great tendency to find such concrete objects in the patterns; it is impossible to prevent her from doing so. Thus, in figure 2 she regards *1* as a roof, *2* as a *Z*, *3* as *V*, *4* as *F* or as a flag, *5* as a steeple and *6* as a little house.

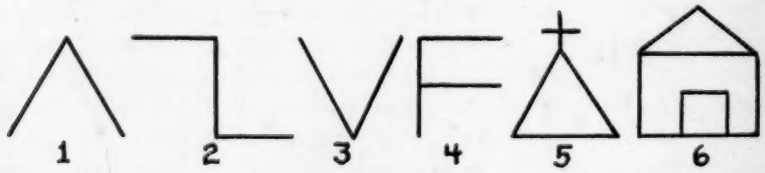


Figure 2

If it is impossible for her to see a concrete and familiar object in the pattern, she fails to reproduce it. It is interesting and elucidating to analyze the errors. The product is often similar to the pattern given; the number of sticks used in reproduction is the same, but instead of the given figure she produces a figure seemingly more simple or more

familiar to her, the last being called a window. Apparently she assimilates strange figures to make more familiar ones; e. g., the figure labeled

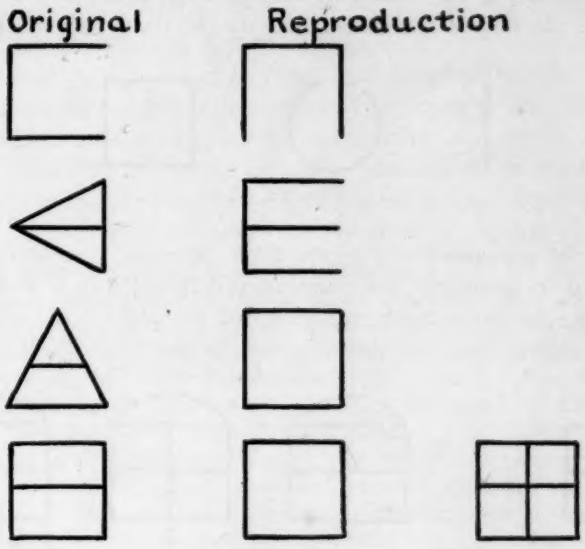


Figure 3

1 she regards as a "Z;" the figure indicated as *2* appears to her as the same "Z," and she will reproduce the latter as *1; 3* she regards as "F;" *4* and *5* she also regards as "F;" *6* she considers to be the figure indicated as *7,* apparently comprehending that the sticks lie at angles to one another but not grasping the relationship between the positions of the individual sticks. She will reproduce this general impression at one time by placing the sticks together in one way, again by placing them in another way.

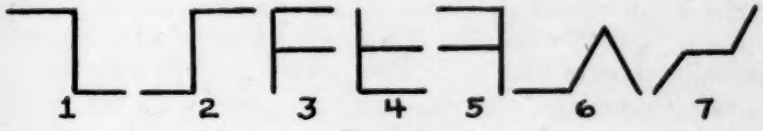


Figure 4

In summarizing, we may say that the patterns are comprehended and reproduced correctly if they represent for the patient concrete objects. The errors seem to point to an understanding of the patterns as apparently known concrete and simple figures. So far as this concrete behavior guides her to the correct goal, she performs well; but when a more abstract attitude is necessary, she fails. What is particularly lacking is comprehension and reproduction of abstract directions.

From the foregoing examples it may readily be seen that not only are comprehension and reproduction changed in this definitely charac-

teristic fashion but memory as well. The patient keeps in mind only those patterns which she is able to comprehend, and for those her memory is satisfactory. The following may perhaps illustrate the situation. There were put before her simultaneously the three patterns shown in

Figure 5

figure 5. She was asked to copy the three patterns. She did this well. When asked to remember the patterns and then to draw them half a minute later, she drew the figure indicated as figure 6, *1*, and a short while later quickly drew the three figures designated as *2*. When asked

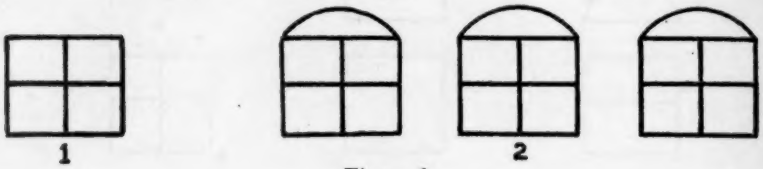


Figure 6

what these meant, she answered: "Windows of a church." It is impossible to have her draw the line, the circle and the square. She draws the square only, with the lines inside, and if the total pattern is lying before her she readily repeats the same square three or four times with equal spaces between them, the distance well proportioned to the size of the windows. Apparently she does not draw senseless squares but three distinct windows of a church in the positions in which they are actually found.

She is able to remember a single line or a circle and to reproduce them later, but only if the pattern is presented alone, isolated from more meaningful patterns, such as the square, which to her is a window. In this case she prefers "concrete" figures, for these alone are the ones which she can remember. Her ability to copy pictures is not bad if the pictures are seen by her as "concrete" figures only. It must also be stated that she does not forget details which may belong to the picture, even to the extent of adding certain details which are not given in the pattern but which seem to her to belong to the object, for example, adding in her copy the windows and door to the figure of a little church without windows and a door. We found this same tendency toward concreteness in behavior during an examination with the pictures of the Heilbronner series.

If she does not understand the meaning of an object, she is unable to do anything with it. In that case she remains unaffected by the

defects of a given picture. She may complete the picture in the sense of the concrete object which she interprets it to mean, but she is totally unable to determine from the given parts, if they do not immediately form a concrete object to her, what the figure may represent, and she will try an entirely different completion of the pattern. At other times it may happen that she well recognizes a pattern which is incomplete, and again she may not comprehend patterns which seem complete. Thus, she is unable to grasp the next to the last picture of the bicycle of the Heilbronner series, in which only the front wheel is lacking. Whether or not an incomplete figure is understood depends on its suitability to awaken in her mind the image of a concrete object.

2. *Behavior to Time.*—The patient is disoriented as to the day, the month and the season. When asked whether the season is warm or cold, she replies: "It is warm here" (meaning in the room). Going to the window and looking out at the snow, she continues: "It is cold." The question, "Which season?" elicits no reply. "Winter or summer?"—"Winter." "How long have you been here?"—no reply. "Have you been here long?"—"Yes." "For weeks?"—"Yes, many weeks." Shortly afterward, in response to the question: "Many days?" the reply was: "Yes, days," with the same certainty. To the question: "Where is your husband?" she answered: "He is gone right now." Shortly afterward she added: "He is living here." She is unable to discriminate between longer or shorter periods of time. She cannot say whether an examination took a long time or a short time.

3. *Perception.*—It is impossible to carry out the ordinary examination for visual acuity. However, by observation in many situations we were able to verify that she discriminates many minor changes in visual objects. Her visual field often appears to be large: at times, she will recognize objects situated entirely in the periphery; at other times she does not see objects which are directly situated within the area of foveal projection. The acuity of her vision and the dimensions of her visual fields depend on her ability to master a task. If she is able to understand a picture at all she will often perceive the finest points of that pattern; on the other hand, when she does not understand a pattern her visual acuity and visual fields seem to be badly disturbed.

4. *Movements.*—The movements of the patient do not show any disturbance. Sitting, walking, grasping or using objects, etc., all seem to be normal. She carries out orders, for example, to show a part of her body, to fetch a certain object, to open the door, etc. Usually she performs the action in a way which demonstrates that the order embodies for her a definitely concrete situation. If she is asked to bring a comb from a table, she will walk to the table, take the comb and comb her hair. When asked to bring a pencil, she takes the pencil and begins to write on a sheet of paper which lies on the table. Actions which have a concrete meaning are continued by her until she is interrupted. For example, she will continue to write as long as she is not prevented or until the paper is filled with writing. This is not a series of senseless perseverations of the same movements. Sometimes, however, there is such a perseveration, particularly if she does not know what she should do at the moment or how she can solve a task. In that case she repeats what she has done previously. However, the previously mentioned perseverance of purposeful actions stops only when they have come to a meaningful end. She combs her hair, but only as long as it may be necessary to complete this task. Then she stops and returns the comb to the table from

which she has taken it. Thus, in the test situations she will utilize ordinary objects correctly from a concrete approach; she does not persevere with the use of one object in one fashion when another use of this object is demanded by the situation. She is at a total loss when asked to do two actions which have no concrete connection with one another or which are not parts of a unit. For example, she is unable to put one of two objects on one table and the other object on another table.

5. *Following Directions.*—The patient does not seem to understand meaningful movements and is unable to imitate them: for example, the movements of threatening or of winking when they are given separately. If they appear in a situation to which they belong, she understands them well and will react accordingly. In the same way she is unable to produce any expressive movements outside of an adequate situation, although they appear normally within an adequate situation. She is unable to demonstrate how a key is used if she does not have one. If she has the key in her hand and is then asked to demonstrate how it is used, she looks around, goes to the door and tries to put the key into the keyhole. If the key fits she executes the movements of locking the door satisfactorily.

6. *Recognition.*—She readily understands complicated pictures, and she usually shows this with many expressive movements. Not seldom she singles out many fine points of the pattern, points to which one normally pays no attention. However, if she is not able to react correctly at the beginning of a task, she will fail. Her words show that she grasps only a specific aspect of the picture—one object or one color—or that her reaction consists of simple general expressions which show that she is unable to derive any meaning or purpose from the situation.

7. *Reading Aloud.*—The patient knows the alphabet and can read the single letters promptly. She reacts similarly to words and often to sentences. For one test several objects as well as some small labels bearing the names of these objects are placed before her on a table. In general, she is unable to succeed at this type of matching test. If by accident the label with the name of an object should be set next to the proper object, she will recognize and associate the two, but we are not sure whether she understands that the label has no other meaning at the time than that of containing the name of the object. To her the two things belong together without her knowing why and how. She is unable in a matching test or in a selection test to associate successfully an object with its printed name, for example, on a slate. She reads the words aloud and then stops. She does not appear able to form any connection between the two items. When shown how to do it she still does not learn. Similarly, she cannot execute a written order, not even so simple an order as to point to her nose, a task which she fulfils immediately when asked verbally. She promptly reads aloud and points correctly to the part of the body in question, but does not seem to understand what she is asked. After several demonstrations she may successfully grasp the association of an object with a written word, but only for a single instance. The next attempt to induce her to do the same is usually without success.

8. *Speech.*—The repetition of words, numbers or sentences on demand is scarcely possible. Contrary to this, she often repeats words or sentences—which she is not asked to repeat—which are accidentally spoken in her presence. It seems that in such situations she understands words and sentences which she did not seem to understand when asked directly. More often, however, she repeats the words picked up in this way without understanding and without any adequate reaction. Her language, as far as motor processes, articulation, etc., are concerned,

is unchanged. Her spontaneous speech is poor, containing many expletives or recurrent utterances, such as, "I don't know," "I know," "I don't like it" and many similar expressive comments.

At the time of the first observation the patient usually spoke English and only occasionally Swedish, her mother tongue. Her English was fluent. However, at a later time it was noted that she did not seem to recognize the fact that she was speaking in another language when she replied in Swedish. When told that we do not understand Swedish, she looked at us as though she had no understanding of what we meant. If she once begins speaking in Swedish it is difficult to induce her to speak in English. Continued speaking in English on the part of the observer may lead her suddenly to revert to English and then to mix English and Swedish haphazardly. She will at times repeat in English what she has previously said in Swedish, apparently translating the words. More thorough examination, however, brought out that she does not understand what translation means and thus was really not translating the words said earlier. It was particularly noticeable that she reverted to Swedish in emotional situations. In examinations some weeks later she spoke only Swedish.

Conversation with the patient became more and more difficult. It did not help to tell her that we do not understand Swedish and to ask her to speak in English. At the time of writing she does not seem to understand what she is being asked. At times she will mix English and Swedish words, but it is impossible to find out with certainty whether she speaks certain words only in English and other words only in Swedish.

It may be said that the patient is usually able to act well if she can act quickly (often unusually quickly), whether she has to repeat a word, to write to dictation, to point to something or to respond to a demand. However, she has the greatest difficulty and fails when there is even a short interval between the stimulus and the response. Properly considered, it is not really the interval itself that makes the performance less correct. At times she will succeed well with a reaction after a longer period has elapsed, and there is no doubt that she can reproduce (in an adequate situation) impressions after a longer interval following the stimulus. The cause of the apparent failure if there is an interval between stimulus and response lies in the fact that the attention of the patient is turned aside during this period; she becomes attracted by another stimulus and reacts to it. Thus, she may react well to the stimulus which has attracted her at the moment, but does not react to the required task; hence her reaction in relation to this task is incorrect. If one wishes to elicit a correct reaction after an interval it is necessary to eliminate all other stimuli or to distinguish between various stimuli, that is, between the stimulus representing the task and those which accidentally intervene and may overshadow that stimulus which demands attention. This demands that one have insight into the differentiation between the stimulus to which one must respond and those stimuli which arise accidentally. This, however, is impossible for her. Thus, one can readily understand the distracting influence of a time interval on her performance. This same factor of distractibility may again be seen in her

inability to complete a task containing different parts, which cannot be solved by a single continuous unitary action but which demands a change of approach on her part, such as going from one element of the problem to a separate element which demands an entirely different approach. In such situations she usually can take the first step correctly; then she either stops or repeats the first response in a way totally inadequate to the solution. She does not stop at the point demanded by the problem. For example, when she was asked to cross out the 3's in a series made up by repetition of three given numbers in the Bourdon test she might cross out the first 3 and then cross out not only the other 3's but all the other numbers as well. When she was asked to underline one of three pictures, she at first responded well, but she did not stop there and continued to underline the other pictures also. This double attitude demanded by the task—for underlining the picture and at the same time leaving the others untouched—is impossible for her to assume. This incapacity gives an understanding of her behavior in different tests.[1]

The patient was able to do simple addition and subtraction problems in writing. After reading the problems, she was able to give the correct answers orally. However, she was unable while reading the problems to write the answers because she was forced to change from an attitude of reading to one of writing. The same experience was repeated with the sentence completion test. She could do the problems orally (to some degree) but was entirely unable to do them in writing. These examples demonstrate clearly that it is not a lack of memory or of a faculty for forming combinations which led to the deficiency but the inability to change from one attitude to another—from one of speaking to one of writing. In order to solve the test orally it is not necessary for her to go from one attitude to another; she started with oral speech and found the result while speaking. In the second task she has to start speaking and then to form the result while writing. She has to transfer from one attitude to another, and because she is unable to do that she fails. In line with our explanation, it is interesting that she solved the completion test (if she was at all able to do so) immediately, while reading, and was apparently unaware of the fact that one of the words in the sentence was not printed, there being a blank. An attempt to make her aware of this fact by asking her to point out the individual words of the sentence failed completely. She could not indicate any single words when asked to do so.

These facts demonstrate that in completing the sentence the patient must always assume the same attitude, and if that attitude is the one needed for a successful result she comes to that result because there is no necessity for a change from the attitude of speaking to that of

1. Dr. Piotrowski carried out the different tests on the patient and permitted us to use the protocols.

forming combinations or of thinking, etc. At the moment in which such a change of attitude became necessary—when she was ordered to write the result, for instance—she failed.

In the Kohs cube construction test the patient's behavior was variable. Sometimes she arranged the blocks quickly so that the colors formed a given design; at times she was unable to do so despite the fact that the design was simple. Closer observation led to the conclusion that she was lacking in the ability to arrange the blocks if she considered the single colors and named them but that she would perform well if she acted without considering or naming the single colors. These facts again find a simple explanation in the assumption that she is unable to change her attitude—for example, from considering the colors and naming them to combining the blocks to form a design. For the same reason she is unable to solve the "digit-symbol" test and other similar types of tests.

This result is of particular interest from the standpoint of judging the effect of a test examination. The sentence completion test is most often utilized for judging the faculty for forming combinations. Examining the patient only orally, one would come to the conclusion that she behaves well in this regard and that she is able to solve this test in the same way as a normal person.

How fast an attitude once taken can be fixed may be seen in the following simple test situation:

> The patient was asked to draw a series of oblong figures (flat ellipses and arrows) in horizontal positions after a short exposure. She did this satisfactorily. Then the same figures were exposed but placed in the vertical direction, and she was again asked to draw them after a short exposure. She persisted in drawing horizontal figures, and no effort succeeded in inducing her to drop this attitude. Similar results were obtained by reversing the order of directions (first vertical and then horizontal).

If one considers these changes of performance in the usual manner, one would describe them in terms such as changes of attention, of memory, of interest, of emotions, of perception or of motion. However, a summary of all these data shows that all these disturbances in the different fields are similar. There is rather a change of the total behavior or a lack of a certain definite behavior which lends a characteristic expression to certain performances and leaves relatively intact certain other performances.

Two types of human attitude toward the world can be distinguished: 1. A concrete attitude, in which one is directed toward given objects and in which thinking and acting are directed by them. Activity is determined directly by the claims which these objects of the environment have. 2. A more abstract attitude, in which one is first moved to think about the objects and is conscious of them. Actions then are

governed not so much by the objects with which one is confronted as by what one thinks about them.

In the first attitude, human behavior is much more passive, in contradistinction to the second, or abstract, type, wherein one partakes more actively in the life around one. Some tasks can be performed only within the scope of the first type of behavior; others, only within the second. In the patient the active, abstract attitude in behavior is lacking, whereas the concrete type of behavior is relatively well preserved. Thus, she performs well in some tasks, namely, in tasks which can be performed by concrete behavior. She fails in tasks which can be fulfilled only by an abstract attitude.

The ability to change one's attitude in accordance with the changing demands of the situation is an expression of this abstract behavior. It is typical of the patient's behavior that she is unable to change her attitude—she cannot perform tasks which demand such changes in attitude.

To understand the patient's behavior it is necessary to remember that she shows a tendency to complete a task as quickly as possible. This characteristic is a typical expression of a person's general desire to avoid situations which may lead to insecurity and anxiety.[2]

Different forms of response to a task can be distinguished: she either solves it correctly or, if she cannot, responds by withdrawing from the situation or by reactions which seem totally absurd. In the second case she will either do or say something to enable her to leave the situation; she will smile or use some simple subterfuge, as "I don't know," "I don't like it" or "How nice it is."

The apparently absurd reactions, on closer analysis, are really correct responses but are correct only in accordance with her own perception of the situation. The reaction will seem absurd to the observer only as long as he does not assume her point of view of the situation.

Comparing the results of the patient's responses with those of patients with lesions of the frontal lobe, one finds a far reaching similarity. There is no doubt that the characteristic picture in cases of lesions of the frontal lobe[3] seems to be much like the behavior of this patient, whom we assume to have Pick's disease.

Two questions arise: 1. Is this statement in agreement with the findings in other cases of Pick's disease, and does our opinion of the psychic alterations meet the interpretations of other authors as to the typical psychic picture in this disease? 2. Is it possible to support the diagnosis of Pick's disease solely on psychic alterations as described by us in this case, and if so, can one generalize?

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2. Goldstein, K.: Der Aufbau des Organismus, den Haag, Nijhoff, 1934, p. 23.

3. Goldstein, K.: Ueber die Funktion des Stirnhirnes, Klin. Wchnschr. **4**: 294, 1926. Goldstein, K.: The Significance of the Frontal Lobes for Mental Performances, J. Neurol. et Psychopath. **17**:27, 1936.

As to the first question, we shall not review the entire literature but shall refer to a few instances. In earlier years, the usual practice was to identify the psychic changes of Pick's disease as disturbances of different individual mental functions. Under the influence of a changed approach to the basic conception of psychopathologic phenomena in recent publications, the opinion that Pick's disease is a systemic deterioration of the function of the cortex of the brain has gained greater sway. Because of this deterioration, the so-called higher performances should be disturbed to a greater degree than the more elementary performances. Accordingly, higher performances alone, such as the ability to form combinations, judgment and orientation in time and space, should be impaired or they should deteriorate to a greater degree than simpler performances, such as perception, activity, memory or elementary attention.

In general, our assumption of psychic change in Pick's disease agrees well with this view. We also agree in considering performances of the higher type as impaired and those of the more primitive as still being retained; however, such an interpretation would be incorrect if it meant that so-called elementary performances are preserved and that only the syntheses of the elementary performances forming the higher processes are impaired. When we speak of higher and lower performances, we mean that a performance is embodied in a higher (abstract) or a lower (concrete) attitude. Thus, a patient cannot be said to have lost the ability to attend or to form combinations, etc., but he is unable to be attentive, etc., in a situation which demands an abstract attitude. In concrete situations all these functions may be normally retained. From this point of view it appears understandable that one can find, in the same patient, symptoms which seem so contradictory—on the one hand, abnormal excitability, unrest, distractibility and lack of interest, bad memory, lack of orientation in space and time, and on the other hand dulness, lack of initiative, abnormally fixed attention, an intense tendency to cling to some objects or actions and good memory in certain situations.

In answer to the second question, Pick's disease may be differentiated from diffuse lesions, at least during the early stages of the disease, by the characteristic difference between the two suggested forms of behavior. In diffuse lesions, the so-called elementary performances usually are also defective. To rule out tumor of the frontal lobes, the symptomatology of which in regard to psychic changes may be closely similar, will not be difficult if one watches carefully the differences in the development of the disease process and the other symptoms characteristic of tumorous conditions. The use of encephalographic pictures will be found especially helpful: in tumor of the brain the change and

displacement of the ventricles; in Pick's disease, the atrophy of the cortex and perhaps a simple dilatation of the ventricles.

At times the greatest difficulty may arise in differential diagnosis between Pick's disease and Alzheimer's disease. As Eugen Kahn and Thompson [4] have pointed out: "No symptom or finding is characteristic of either disease." Only the consideration of the total picture can help. Of particular importance may be what we have set forth as to the difference between the two forms of behavior in patients with Pick's disease. This difference is usually not so distinctive in Alzheimer's disease. In the latter the "primitive" performances as well are disturbed early. Further it may be said that in this condition more symptoms may be noted which indicate differently circumscribed lesions; thus, in this disease focal signs and convulsions are frequent; they are absent in Pick's disease, apart from symptoms of sensory aphasia, which as sequelae to atrophy of the temporal lobe are not uncommon in Pick's disease. If such disturbances of language do appear, however, they concern more the "higher" functions of language, while in Alzheimer's disease, the "speech-material" is more deeply involved. A valuable diagnostic aid is given by the encephalogram when it shows the characteristic circumscribed areas of atrophy, as in our case. Changes in the encephalogram in Alzheimer's disease will be found to be more concerned with the entire cortex of the brain.[5]

CONCLUSIONS

The possibility of utilizing the psychic changes for the diagnosis of Pick's disease is greatly enhanced in the early stages of the illness, at a time at which the aforementioned differences in behavior are clear. Later, also, the "primitive" functions become more and more involved, and differential diagnosis with reference to the diffuse processes becomes more difficult. However, at this stage also the difference mentioned may become manifest in the sudden appearance of some words or actions which show that the patient, apparently totally confused, can still react adequately in special situations. In this stage of the disease, the anamnesis will become especially important if it is possible to conclude from its data that at the very first stage of onset the characteristic difference was present. In any case, consideration of the symptomatology typical of disorders of the frontal lobe will aid greatly in the diagnosis of Pick's disease.

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4. Kahn, E., and Thompson, L. J.: Concerning Pick's Disease, Am. J. Psychiat. **13**:937, 1934.

5. Flügel, F. E.: Die Encephalographie als neurologische Untersuchungsmethode, Ergebn. d. inn. Med. u. Kinderh. **44**:327, 1932.

WORD ASSOCIATIONS AS AFFECTED BY DEFICIENT OXYGEN, EXCESS OF CARBON DIOXIDE AND HYPERPNEA

ERNST GELLHORN, M.D., PH.D.
AND
SAMUEL H. KRAINES, M.D.
CHICAGO

In preceding papers Spiesman and one of us (E. G.)[1] have reported the effect of hyperpnea, lack of oxygen and excess of carbon dioxide on several cortical and subcortical processes. Since it is known that a reduction in the oxygen tension in the inspired air leads to characteristic mental symptoms[2] and since similar symptoms were observed in our experiments with carbon dioxide and hyperpnea,[3] it seemed desirable to investigate the influence of these factors on certain measurable cortical processes which are associated with what are ordinarily termed psychic phenomena. A suitable method should allow one to study quantitatively the alteration of the fundamental process and furthermore should also reveal the qualitative changes which will occur under experimental conditions. We thought that the method of studying associations would fit our purpose best for the following reasons:

1. Association processes may be considered to be fundamental in practically any type of mental activity.

2. Studies with association tests in patients with lesions in the brain seem to indicate that "there is a parallelism between the psychic state and the degree of disturbance in associations" (Stern)[4].

3. The association test in the form developed by Kent and Rosanoff[5] lends itself to a quantitative and qualitative study.

4. Norms have been established for this test for normal and for certain pathologic conditions.

From the Department of Physiology and the Psychiatric Institute, University of Illinois, College of Medicine.

1. Gellhorn, E., and Spiesman, I. G.: Am. J. Physiol. **112**:519, 620 and 662, 1935.

2. The literature is adequately summarized by McFarland, R. A.: Arch. Psychol., 1932, no. 145.

3. Compare also Rosett, J.: Brain **47**:293, 1924.

4. Stern, E.: Arch. f. Psychiat. **57**:725, 1917.

5. Kent, G. H., and Rosanoff, A. J.: Am. J. Insanity **67**:37, 1910.

It seemed desirable to carry out such work on a broad basis, which would enable us not only to compare our results with those obtained in various clinical conditions by Kent and Rosanoff but might also furnish a basis for a quantitative study of these functions in instances of injuries to the brain. Since it is known through the investigations of Lowson [6] and Wespi [7] that the association time is lengthened when there is a lack of oxygen, we did not, except in a preliminary group, concern ourselves with the association time. Our attention was directed to the determination of the type of association response and to a quantitative evaluation on the basis of Kent and Rosanoff's tables.

The problem investigated may be stated as follows:

1. What is the effect of lack of oxygen, excess of carbon dioxide or hyperpnea on the type of association?

2. How do the changes observed under these experimental conditions compare with those obtained in mental disease and injury to the brain?

3. Are there specific differences between the three experimental conditions investigated?

METHOD

The Kent-Rosanoff test may be best described by the following quotation [5]: "The stimulus consists of a series of one hundred spoken words, to each of which the subject is directed to react by the first word which it makes him think of. From the records obtained from these normal subjects, including in all 100,000 reactions, we have compiled a series of tables, one for each stimulus word, showing all the different reactions given by one thousand subjects in response to that stimulus word, and the frequency with which each reaction has occurred."

We proceeded in such a fashion that the experimental subject was given a sheet with numbers from 1 to 100. The stimulus words were dictated to him, and he wrote his answers after the corresponding numbers. In the first group of control experiments twenty-five normal persons (medical students) were given such a test. The answers were evaluated on the basis of the standardization of Kent and Rosanoff, and thereby the usualness of response was determined for all the associations. These were then grouped in a fashion indicated in table 1. One sees from this table that the distribution of the words in the various groups remained practically unchanged when it was compared in regard to the first and the second fifty words. The reliability of the test is therefore high. Although such great constancy was not present in every case, the comparison of the reactions to the first fifty words with that to the second fifty shows an almost ideal agreement when the total material from all twenty-five experimental subjects (chart 1) is added (compare also table 1 *A*).

After the reliability of the control test was established, we carried out experiments with lack of oxygen, hyperpnea and excess of carbon dioxide. As in the experiments reported previously, the gas mixtures were prepared in Douglas bags, from which the experimental subjects inhaled for about ten minutes.

6. Lowson, J. P.: Brit. J. Psychol. **13**:417, 1923.
7. Wespi, H.: Arbeitsphysiol. **7**:484, 1933.

Ordinarily the test began after the subject had been under the influence of the gas for from three to four minutes. In the experiments with hyperpnea the experimental subjects breathed maximally according to the rhythm of a metronome at a rate of 35 per minute for two minutes, and immediately thereafter the association test was carried out. Every one of these experiments was preceded by a control test. In some experiments the first fifty words and in other experiments the second fifty words were used as a control, without influence on the results. To avoid the effects of practice, the test was not repeated with the same subject.

RESULTS

The first group of experiments concerns the influence of lack of oxygen on associations. A total of forty-five experiments were carried

TABLE 1.—*Summary of all Control Experiments*

	Frequency	0 and ±	1 to 15	10 to 100	Over 100
A 25 subjects tested in a group	First 50 words.....	127	236	314	541
	Second 50 words.....	131	234	311	535
	$\frac{\text{Second 50 words}}{\text{First 50 words}} \times 100$.....	103%	98%	98%	98%
B 20 subjects tested individually	First 50 words.....	112	205	252	431
	Second 50 words.....	105	194	265	435
	$\frac{\text{Second 50 words}}{\text{First 50 words}} \times 100$.....	94%	95%	105%	101%

TABLE 2.—*Summary of all Experiments Involving Lack of Oxygen**

Frequency	0	1 to 15	16 to 100	Over 100
Totals of all (29) control experiments.....	147	273	375	640
Totals of all (29) experiments with lack of oxygen	185	291	394	554
$\frac{\text{Lack of oxygen}}{\text{Control}} \times 100$.....	126%	107%	105%	87%

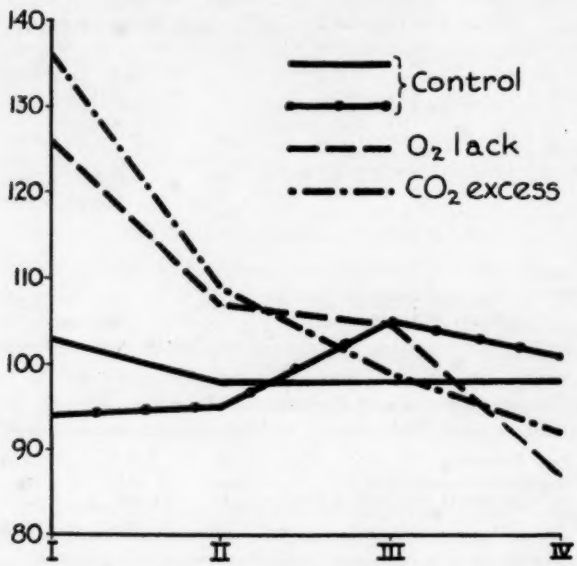
* In each experiment fifty words were used under control conditions and fifty under lack of oxygen.

out, in which the subjects, mostly students and staff members, inhaled a mixture of gases containing between 7.3 and 11 per cent of oxygen for about ten minutes from Douglas bags. A typical experiment shows that under the influence of lack of oxygen there is a shift in the usualness of response which is characterized by an increase in the number of individual responses at the expense of the common responses. Another shows that the "shift to the left" [8] is not restricted to the group of individual responses but involves several other groups. The results obtained from twenty-nine experiments indicate a marked shift to the left with lack of oxygen (chart 1 and table 2).

8. The phrase "shift to the left" will be used hereafter to indicate an increase in the number of individual response (O group) at the expense of the more common responses (table 2).

Before we discuss further the experiments dealing with lack of oxygen, we shall describe similar experiments in which our subjects inhaled a mixture containing from 6 to 7 per cent of carbon dioxide. This condition, too, is accompanied by an increased unusualness of response (shift to the left) in a manner similar to that observed in the experiments dealing with a lack of oxygen.

In the last group of experiments the effect of hyperpnea was studied. The test was carried out after the cessation of the period of hyperpnea. In spite of the decided disadvantage that the test was taken in a time interval during which the effects of the hyperpnea gradually disappeared, a shift to the left was noticeable. There seems, however, to be some



The ordinates indicate the change in frequency of response between the first and the second fifty words, expressed in percentage of the former. The abscissas represent: *I*, individual responses; *II*, *III* and *IV*, responses with the frequency of 0, 1 to 15, 16 to 100 and more than 100, respectively. The control experiments indicated by the solid line were made with twenty-five subjects. The other control experiments were made with twenty subjects who breathed through a mouthpiece ordinary air from a Douglas bag during the test carried out with the second fifty words.

deviation from the type observed when there is a lack of oxygen and an excess of carbon dioxide, in that there is a shift from the group of most common reactions (group 4) to group 3 and from group 2 to group 1.

Since the possibility existed that the discomfort caused by a mouthpiece and the apprehension of effects induced by the inhalation of the

gases might alter the frequency of the response in the word association test, another control series was carried out with twenty freshman medical students who had not been subjected to the test before. They were given the first fifty words under control conditions (without breathing through a mouthpiece), whereas they breathed from a Douglas bag filled with air when they carried out the association test with the second fifty words. The experimental subjects were told that they were subjected to lack of oxygen in this experiment. In spite of these conditions no shift to the left occurred; in fact, the percentage of individual responses was slightly (6 per cent) decreased in comparison with that for the control group (chart 1 and table 1). These control experiments prove beyond doubt that the shift to the left is the result of a characteristic effect on word associations of the gases inhaled. The control experiments as well as those involving a lack of oxygen, and excess of carbon dioxide and hyperpnea were subjected to statistical analysis with the chi-square distribution test. The results presented

TABLE 3.—*Statistical Analysis of the Results*

	X^2	P
Control group A	0.24	0.95
Control group B	1.74	0.60
Group with lack of oxygen	26.19	0.00003
Group with excess of carbon dioxide	14.78	0.002
Group with hyperpnea	10.48	0.01 to 0.02

in table 3 indicate that the changes obtained under experimental conditions are statistically significant.[9]

In analyzing the word associations in detail we did not find it profitable to classify the reactions in many subgroups (as Woodworth and Wells[10] and Kent and Rosanoff[5] did). Two phenomena are conspicuous in all experiments—one is the phenomenon of perseveration and the other that of dissociation. Under the first we include the repetition of the same word as an answer to several stimuli. Such perseveration occurs to a certain degree even in control experiments and shows wide individual differences. However, in all our experimental groups lack of oxygen, excess of carbon dioxide and hyperpnea increased the number of perseverations considerably, as is evident from table 4. In view of the slight variations in the number of perseverations in our control experiments, the increases obtained with lack of oxygen and the other experimental conditions are significant. However, not only did the number of perseverations increase 50 per cent and more on the

9. Fisher, R. A.: Statistical Methods for Research Workers, London, G. E. Stechert & Company, 1928, p. 77.

10. Woodworth, R. S., and Wells, F. L.: Association Tests, Psychological Monographs, Baltimore, Williams & Wilkins Company, 1911, vol. 13, no. 57.

average owing to the experimental factors under investigation but the type of perseveration changed. In control experiments we find in general that a word is not repeated more than once and that only in a few cases may two repetitions of the same word occur. When there is a lack of oxygen we notice not only that the total number of responses showing perseveration increases but that the number of times that one word is used is increased. It is of particular interest to note that these changes in perseveration increase with an increasing degree of lack of oxygen. In the experiment carried out with one of our subjects one can recognize not only the increase in the number of perseverations when the concentration of oxygen inhaled decreased from 9.8 to 8.7 per cent and to 7.9 per cent but also an increase in the number of repetitions of the same word.[11] Similar observations were made under the conditions of excess of carbon dioxide and hyperpnea.

TABLE 4.—*Summary of Observations on Perseveration*

I	24 control experiments		
	Perseverations in first group	89	
	Perseverations in second group	83	Decrease 7%
II	45 experiments with lack of oxygen		
	Perseverations in control group	222	
	Perseverations in group breathing insufficient oxygen	334	Increase 50.5%
III	22 experiments with excess of carbon dioxide		
	Perseverations in control group	94	
	Perseverations in group breathing excess of carbon dioxide	148	Increase 57%
IV	16 experiments with hyperpnea		
	Perseverations in control group	77	
	Perseverations in group with hyperpnea	127	Increase 65%

Another group of reaction words may be noted. Under the experimental conditions studied not infrequently nonspecific associations occur, such as "good," "bad," "color," "man" and "well." We give a few examples of the type and frequency of the occurrence of these nonspecific associations, which were rare or absent in control experiments. In one experiment with 6.25 per cent carbon dioxide the following nonspecific associations were recorded:

Stimulus Word	Reaction Word
play	well
candy	bad
summer	soon
money	well
habit	bad
accomplish	well
sin	where

11. We did not deviate in these experiments from our principle of not repeating the same association test but used another group of 100 words as stimulus words, which are being standardized on 1,000 subjects under control conditions at the time of writing.

It is noticeable from this record as well as from many others that the nonspecific reactions show many perseverations. In an experiment with 9.6 per cent oxygen the following nonspecific reactions were given:

Stimulus Word	Reaction Word
sin	do
pray	do
fall	do

In an experiment with 8.7 per cent oxygen the reaction was:

Stimulus Word	Reaction
danger	bad
pride	bad
play	long
sin	long

Another subject reacted under the influence of 8.6 per cent oxygen to the stimulus words "comfort," "working" and "trouble" in every instance with "no," although this word was never used in the control period.

Similar reactions were also found with hyperpnea, as the following record shows:

Stimulus Word	Reaction
hungry	not
thirsty	not
loud	not loud

Another peculiar change in the type of association was observed several times in experiments involving lack of oxygen and never occurred in any of our control experiments. The experimental subjects used a foreign language in their association words. In one case, when a subject was breathing a mixture containing 8.9 per cent oxygen, the association to "bird" was *"oiseau"* and that to doll, *"poupée."* In another case the stimulus "finger" was given and the association of the subject to this word was "hat." He explained afterward that he had thought of an English translation of the German word *"Fingerhut."* None of these subjects were particularly versed in the use of the foreign language which influenced their associations under experimental conditions. Not infrequently misspelling occurred, although it was absent in the control experiments. Furthermore, it was noted that stimulus words were misunderstood, although under the same set of circumstances such misunderstandings rarely occurred in the control experiments.

All the changes in association described so far are quantitatively but not qualitatively different from associations which occur under normal circumstances. The next group of associations, however, is

of an entirely different nature. We consider them as dissociations because there is no obvious relationship to the stimulus word applied. Although there may be a gradual transition from individual responses to dissociations, the separation of the two groups is justified for practical reasons, since such dissociations occur only in rare instances in control experiments. These dissociations were observed in fourteen of forty-five experiments with lack of oxygen but only twice in twenty-one experiments with hyperpnea. As far as the experiments with carbon dioxide are concerned, dissociations were absent, although numerous unspecific reactions and perseverations occurred. These facts seem to point out definitely that the mental changes observed are most severe with lack of oxygen and least marked with an excess of carbon dioxide. Whether dissociation may occur under the influence of carbon dioxide, provided that it is administered for a sufficient length of time, remains to be seen.

In most cases the classification of a word as a dissociation was determined by the fact that neither the experimenter nor the experimental subject could find any explanation for the choice of the reaction word. Although most associations belonging to this group have therefore only the fact in common that the reaction words cannot be grouped under any "understandable" heading, it may be mentioned that occasionally reaction words occurred in which clang associations seemed to determine the reaction. For instance, in an experiment in which the subject breathed 8.9 per cent oxygen, the following reaction was obtained:

Stimulus Word	Reaction Word
black	blank
short	show

In another experiment a similar response was observed when the subject reacted to the stimulus word "wild" with the association "mild."

In view of the great pathologic significance of dissociations and their occurrence in mental disease, it seems to be appropriate to give a few examples. It is clear that the separation of dissociations from "understandable" reactions is a transitory one; but even if one admits that occasionally some reactions which we have classed as dissociations may raise some doubt as to the justification of this classification, we are certain that our experiments, as a whole, prove undoubtedly: first, that dissociations occur under the conditions of lack of oxygen and to a slighter extent after hyperpnea; and second, that with decreasing concentration of oxygen not only do the bodily symptoms become more severe but the mental disturbances apparent in the number of dissociations increase. For instance, in an experimental subject who did not show any dissociations in fifty control words three dissociations

occurred under the influence of 9.5 per cent oxygen and twelve under the influence of 8.7 per cent. In another case, dissociations were absent in a control experiment as well as with 9.8 per cent oxygen. Three dissociations occurred in fifty words after the student had been subjected to 8.7 per cent oxygen, and 9 dissociations occurred during an experiment with 7.9 per cent oxygen.

During the experiments with lack of oxygen, excess of carbon dioxide and hyperpnea a number of somatic symptoms were observed. They were most marked with lack of oxygen, particularly with low concentrations, but also apparent under conditions of hyperpnea and of excess of carbon dioxide. They were mainly dizziness, a feeling of

TABLE 5.—*Dissociations Under Lack of Oxygen*

Experimental Subject	Oxygen Concentration, Percentage	Stimulus Word	Association Word
He.	7.3	sin	full
		brick	anew
		button	sweat
		fall	sweep
Go.	8.7	part	eat
		mercy	habit
		false	alive
		anxiety	think
		choose	think
		ridicule	think
		nice	glad
Ma.	9.9	Bible	well
		bath	color
		priest	color
		religion	tired
		thirsty	tired
		square	rough
		loud	could
C.	8.0	health	ready
		bath	heart
		cottage	heart
		sheep	lamp

warmth, decrease in vision and hearing, and tremor. When subjected to a lack of oxygen the experimental subjects complained frequently of fulness of the head and felt "light headed." When the oxygen was reduced below 9 per cent, the symptoms became more severe in the majority of cases. Nausea was, in general, a fairly rare symptom. However, dizziness, severe perspiration, tremor, weakness, sleepiness, ringing in the ears, cyanosis and extreme paleness of the skin were frequently observed. Writing was not infrequently severely disturbed, as was also found by McFarland and Wespi. In some cases it was surprising to observe that a person obviously near the threshold of fainting, who, on account of the extreme weakness of the hand and tremor of the fingers, was able to write only after many unsuccessful starts, finally managed to give a completely normal association. On the other hand, we noticed a number of cases in which the experimental subjects

showed only comparatively slight somatic symptoms and fairly good coordination in writing movements, together with severe changes in associations (occurrence of frequent perseverations and dissociations).

COMMENT

The chief result of this work consists in the observation that under the influence of lack of oxygen and excess of carbon dioxide and to a lesser degree after hyperpnea a shift in the usualness of response of association words occurs, so that the more commonly used reactions are diminished in favor of individual and less common reactions. Furthermore, it was observed that the association time was lengthened. This was most marked with severe lack of oxygen but was also present in experiments with excess of carbon dioxide and with hyperpnea. Finally, it may be stated that under experimental conditions perseverations occur with increasing frequency and that with lack of oxygen and to a much lesser extent after hyperpnea even apparently senseless reactions (dissociations) appear.

In an attempt to express this result in physiologic terms and to evaluate it in the light of clinical experiences, we may say that the common associations elicited by a stimulus word are the result of experience during the individual life. As in any other stimulus-reaction relationship, one may assume, as Verworn [12] did, in regard to learning and memory processes that the resistance of the pathways between those cortical parts involved in the perception of the stimulus word and those on the excitation of which the reaction depends is lowered (facilitation). The establishment of such patterns would account for the predominance of the common reactions in normal persons. The common reactions have become most specific to the stimulus word, leading to the exclusion of many other possible reactions. A similar "learning" process seems to occur during the development of conditional reflexes. Whereas the conditioned stimulus may evoke a great diversity of muscular responses (orientation reaction) in an early stage of the formation of conditioned reflexes, the increasing facilitation between the "centers" of the "unconditioned" and the "conditioned" stimulus produces a most selective and predictable response when the conditioned reflexes are established. With lowered excitability, however, e. g., during the extinction of a conditioned reflex, this selectivity is lost and much more varied responses, in fact, entirely new types of responses, may ensue (Beritoff [13]). Similar are the conditions in our association experiments when under conditions of reduced excitability (lack of oxygen, etc.) the number

12. Verworn, M.: Ztschr. f. allg. Physiol. **15**:413, 1913.

13. Beritoff, J.: J. f. Psychol. u. Neurol. **33**:113. 1927.

of the unpredictable (individual) reactions increases. The high selectivity of the response is a function of the integrative action of the cortex, and it is not surprising, therefore, that it is lessened with lack of oxygen. This interpretation seems to explain equally well the alterations in associations studied in this paper, as well as the changes in personality observed in high altitude and prolonged low pressure chamber experiments.

Our experiments confirm and expand considerably the recent work of Wespi, who studied in a low pressure chamber the influence of various reductions of barometric pressure on associations with Jung's test. He found not only a delay in the reaction in the association time in most experiments but the occurrence of perseverations and dissociations.

Because of the use of the same test, the results of our experiments are most readily compared with those obtained by Kent and Rosanoff for persons with mental disease. As table 6 indicates, these authors observed in "insane" persons with various forms of mental disease a

TABLE 6.—*Distribution of Associations After Kent and Rosanoff*

	Individual Reactions, Percentage	Common Reactions, Percentage
1,000 normal persons	6.8	91.7
247 insane persons	26.8	70.7

decrease in the common reactions and an increase in the individual reactions corresponding to what we have found with lack of oxygen, excess of carbon dioxide and hyperpnea. Moreover, although the disturbance in association was, of course, much more severe in the patients with mental disturbances than even in those of our experimental persons who were most severely affected by lack of oxygen, it is obvious that the type of change involved was similar in mental disease and in our experiments with lack of oxygen. The authors stated that: "Some of these tendencies when appearing at all prominently are so highly characteristic of dementia praecox as to be almost pathognomonic." The tendency of their patients to give (1) neologisms or (2) reactions largely of the incoherent type and the tendency toward (3) stereotypy (perseveration) make it clear that although the causes of these conditions in our experiments and in mental disease may have nothing in common, the method involving the lack of oxygen enables one to produce conditions which affect psychic phenomena in a fashion similar to that of mental disease. It will be the object of further experimentation to find other factors which are of similar fundamental importance to the maintenance of normal psychic functions.

In addition to Kent and Rosanoff's study of persons with mental disease, investigations by Eastman and Rosanoff [14] of feebleminded children and by McElwee [15] of subnormal adolescents show also increases in the number of individual responses above those in normal controls. These were indeed marked in McElwee's cases. Moreover, in this group dissociations occurred which were absent in Eastman and Rosanoff's patients, although perseveration was observed. This seems to justify the assumption of a gradation in the disturbance of associations in clinical cases which, starting with moderate increases in the number of individual reactions and some perseveration, leads to a considerable shift to the left with frequent perseveration and the occurrence of dissociation. It seems to us of particular interest that a similar gradation may be obtained experimentally by subjecting a person to various degrees of lack of oxygen.

SUMMARY

In order to study the influence of lack of oxygen, excess of carbon dioxide and hyperpnea on associations the Kent-Rosanoff test was employed and studied on more than one hundred persons. It was found that:

1. In all three conditions there is a shift in the usualness of the response, so that the number of individual reactions increases. These changes are statistically significant.

2. In all three conditions nonspecific reactions and perseveration occur in a much higher degree than in corresponding control experiments.

3. Under the conditions of lack of oxygen and to a much slighter extent in hyperpnea, apparently senseless associations (dissociations) are formed, which are comparable to those observed in mental disease.

4. The severity of these mental changes increases pari passu with the decreasing concentration of oxygen. There seems to be a lack of parallelism between the degree of mental disturbance and the severity of somatic symptoms.

DISCUSSION

DR. D. M. OLKON: Dr. Kraines' series of experimental stimulus words and their responses was interesting. He stated that the irrelevant responses represented vicarious answers which were due to the confusion resulting from anoxemia of the brain. He attributed this anoxemia to the lack of oxygen and excess of carbon dioxide brought about by the experiment. He also advanced the theory that similar anoxemia of the brain must exist in patients with psychosis and asserted that similar confusion of words and responses is encountered particularly in association with schizophrenia. He contended that a test of this type (stimulus word and responses) can serve to determine the type of psychosis.

14. Eastman, F. C., and Rosanoff, A. J.: Am. J. Insanity **69**:125, 1912.

15. McElwee, S. W.: Am. J. Psychiat. **11**:311, 1931.

One wonders, first, how he knows that anoxemia of the brain exists in the psychoses, how long it lasts, the degree of intoxication which it causes and how it is causal in the mechanism of stimulus and response of words. Second, the responses to the table of words purported to be criteria seem for the most part to be relevant and consistent rather than irrelevant answers. For example (stimulus word) "habit" (answer) "poor;" "false," "man;" "grief," "woman;" "lie," "boy;" "anxiety," "man" and many other answers seem adequate. The entire category of such responses depends so much on former experience, habits of thought, education, memory, attention, etc., that one fails to see the significance of such a measuring device for diagnosis of the psychoses. That patients with psychosis present various confusions of words, irrelevant answers to words and a great many other mental discrepancies need not be emphasized here. But the statement that such comparative studies can be used as criteria for differentiating the types of psychosis is to be taken with reservation.

DR. CLARENCE A. NEYMANN: I have employed many psychologic tests. A basic condition for every test, and, indeed, for the Kent-Rosanoff test, is that the patient shall not be subjected to external stimuli of any kind while he is being tested. It is my understanding that these patients were under maximum external stimulation during the test period. I wish to know if Dr. Kraines examined and tested the same group while subjecting them to entirely different but equally severe external stimulation without lack of oxygen or increaase of carbon dioxide. I have employed the Kent-Rosanoff test in the examination of patients who were not suffering from psychosis but had artificially induced febrile states. Abnormal responses were elicited because, I believe, the great physical discomfort changes the psychic reactions, without any special reference to increase in carbon dioxide or lack of oxygen. Before Dr. Kraines draws any conclusions, I believe he should subject the same persons to various and at least as intense psychic stimuli as those he has described. When this has been done he may better judge the true effect of a lack of oxygen and an increase of carbon dioxide.

I may add that the Kent-Rosanoff test has been thoroughly standardized. Dr. Kraines has merely shown that it does not function when the patient is subjected to severe external stimuli. This fact was well known. Nothing unusual or new has been demonstrated.

DR. MEYER SOLOMON: Were the changes different from those one would find in mental fatigue from any cause? In other words, would not any state of overstrain to the organism in general produce a somewhat similar result? Has any comparative work been done on patients in normal conditions?

DR. LEWIS J. POLLOCK: I wish to ask a question that relates to the mechanism of response to stimulus in relation to associated processes. In order to determine the response one must first determine whether the subject received a stimulus. What criteria were used to determine that the subject was stimulated by the words? Haldane, in his experiments, persisted in the response, keeping it at "38" or some such number, when he was questioned or instructed from without the chamber in which he was enclosed. This response may have been the result of not understanding what was said and not of difficulty of association.

DR. S. H. KRAINES: Dr. Olkon's attempt to draw understandable relations between certain stimulus words and their responses which, in the light of possible logical connections, we have called dissociations, does not hold here. It is possible to draw such relationships between almost any two words, if one tries hard enough. In our experiments a response was considered a dissociation if neither the examiner nor the subject could give a reason for the response. This is an arbitrary definition; yet, with this rule in mind, we found practically no dissociations in the control experiments and a persistent increase in dissociations with decreasing oxygen intake.

Dr. Neymann's suggestion is a good one. It is possible that the brain, when subjected to any type of severe stress, will give responses similar to those we obtained. As a fact, by investigation of three conditions—hyperpnea, excess of

carbon dioxide and lack of oxygen—we obtained essentially similar results. In the same way Dr. Solomon's suggestion may be evaluated.

DR. LEWIS J. POLLOCK: If I say the word "man" and you respond with the word "people" and I say "woman" and you say "people" and I say "child" and you say "people," I must establish that the word was a stimulus, that is, that the meaning of the word was understood. This was what I asked you, did you determine that the word was a stimulus? I have a cat, and she scratches the legs of the dining-room table. Her name is Kozie, and if I say "Kozie!" she stops scratching. If she does it again and I enunciate any other combination of syllables similar to "Kozie" with the same inflection of my voice she also stops. This is because she understands not the word or words but the rhythm, inflection, etc. In man the meaning of the word itself must be understood before one may say that the stimulus to response is that particular word.

DR. S. H. KRAINES: In cases in which the response to the stimulus word was understandable and was found in the Kent-Rosanoff tables, there can be no doubt about the relationship between the stimulus word and the response. In the case of dissociation and perseveration, the natural link between the stimulus word and the response is broken. This seems to be characteristic of some mental conditions, as well as of the conditions studied in this paper.

INVOLUTIONAL MELANCHOLIA

TREATMENT WITH THEELIN

PURCELL G. SCHUBE, M.D.

M. C. McMANAMY, M.D.

C. E. TRAPP, M.D.

AND

G. F. HOUSER, M.D.

BOSTON

Although the psychoses starting during the period of involution were recognized and their relationship to this period was declared, it was not until 1896 that Kraepelin [1] definitely described melancholia and classified it as an involutional or a retrograde presenile process (*das Irresein des Rückbildungsalters*). In 1899 he [2] described it as a distinct entity occurring in the involutional period of life and as more frequently present in women than in men. This concept, with insignificant variations, has stood since, in spite of the repeated attacks, starting with those of Thalbitzer,[3] in 1905, and of Dreyfus,[4] in 1907, which have been directed against it.

Recently, the concept of involutional melancholia has been more firmly established by the clinical experience of Noyes,[5] who pointed out that persons showing an involutional psychosis have personalities the outstanding characteristics of which are inhibition, seriousness, rigidity, overconscientiousness and no sense of humor. The patient often has had a routine of life which was narrow, somewhat stereotyped and devoid of diversions; frequently, he has been a loyal subordinate, meticulous as to detail and unaggressive. Titley,[6] studying a group of ten cases of involutional melancholia, verified the experience of Noyes.

From the Psychiatric Clinic of the Boston State Hospital.

1. Kraepelin, E.: Psychiatrie, ed. 5, Leipzig, J. A. Barth, 1896.

2. Kraepelin, E.: Psychiatrie, ed. 6, Lepzig, J. A. Barth, 1899.

3. Thalbitzer, quoted by May, J. V.: Mental Diseases, ed. 1, Boston, Richard G. Badger, 1922.

4. Dreyfus, G. L.: Die Melancholie ein Zustandbild des manisch-depressiven Irreseins, Jena, G. Fischer, 1907.

5. Noyes, A. P.: Modern Clinical Psychiatry, ed. 1, Philadelphia, W. B. Saunders Company, 1934.

6. Titley, W. B.: Prepsychotic Personality of Patients with Involutional Melancholia, Arch. Neurol. & Psychiat. **36**:19-33 (July) 1936.

He found that the prepsychotic personality of persons in whom involutional melancholia develops shows a narrow range of interests, difficulty in adjusting to change, limited capacity for sociability and friendship, rigid adherence to a high social ethical code, marked proclivity for saving, reserve that becomes positive reticence as far as intimate matters are concerned, an ever present anxious tone, profound stubbornness, overwhelming overconscientiousness and strained meticulosity as to person and vocation—in brief, the anal-erotic type of personality.

Treatment of this involutional psychosis has run the gamut of therapy, and varying successes have been reported—none of which is of any specific or definite value. Recently, however, there has been reported in a series of papers a rather remarkable incidence of improvements in cases of involutional melancholia due to the use of an endocrine product, theelin.

The first paper was published in 1934 by Werner [7] and his associates. They noted improvement in all of a group of nine patients. Of a second group of eleven patients there was improvement in nine and no improvement "as yet" in two. In the combined groups the total number who were improved was eighteen, or 90 per cent.

After this paper Werner [8] and his associates published another report on the treatment with theelin of twenty-one patients with involutional melancholia. They did not make it clear whether or not the patients used in the first study formed a part of the second group treated but of these twenty-one patients there was improvement in 19, or in 80 per cent.

A number of months before the publication of Werner's work, we had started an investigation of the value of theelin in the treatment of involutional melancholia, and in view of the remarkable results obtained by Werner and his associates, we feel it incumbent on us to publish our data. It is our purpose in this paper to do so.

METHOD

The patients used in this study were carefully selected by us as presenting cases of involutional melancholia. Each patient was then given 1 cc. of theelin in oil (300 rat units, Doisy) intramuscularly three times a week for ten weeks. It was believed that if there was to be improvement in the patient due to theelin, it would manifest itself in some manner within that time. Furthermore, it was decided that if improvement did manifest itself, the treatment would be continued

7. Werner, A. A.; Johns, G. A.; Hoctor, E. F.; Ault, C. C.; Kohler, L. H., and Weis, M. W.: Involutional Melancholia: Probable Etiology and Treatment, J. A. M. A. **103**:13-16 (July 7) 1934.

8. Werner, A. A.; Kohler, L. H.; Ault, C. C., and Hoctor, E. F.: Involutional Melancholia: Probable Etiology and Treatment, Arch. Neurol. & Psychiat. **35**:1076-1080 (May) 1936.

until recovery occurred. The cases were studied from the laboratory, the physical and the medicopsychiatric point of view for the period of treatment and for months following it. During this time no other form of therapy was resorted to.

The group used as a control was twice the size of the group treated with theelin and consisted solely of patients with involutional melancholia. All received other types of available hospital therapy, but no theelin.

RESULTS

Group Used as a Control.—This group consisted of twenty patients. The ages ranged from 40 to 55 years. There were six men and fourteen women. Of these patients who received no theelin but, instead, other available hospital therapy, two men and two women improved sufficiently to leave the hospital and have been considered as recovered. Thus, in the group used as a control the incidence of recoveries was 20 per cent.

Group Treated with Theelin.—There were ten patients in this group. The ages ranged from 38 to 58 years. Four were men and six, women. In none of the ten patients treated with theelin was there evidence of any type of improvement in the mental condition.

The mental and physical condition of three of the patients (T. D., G. N. and T. L.) became definitely worse during the treatment; one patient (T. D.) died. One of the patients (T. L.) continued to grow worse until the treatment was discontinued and then gradually reverted to his original mental state.

In one patient (I. McM.) regular monthly periods were established after four weeks of treatment with theelin. There was no alteration in the mental condition.

No changes were noted in the hair, the texture of the skin, the breasts or the genitalia of any patient. There was no change in the appetite or the sleep rhythm of any patient. In two (G. N. and T. D.) there was a definite loss of weight.

In one patient (G. N.) during treatment there was marked retention of urine, necessitating catheterization; this man also had uncontrollable diarrhea.

The blood pressure, the pulse rate and pulse pressure, the blood picture and the urinary picture remained unchanged in every case. The sedimentation rate of the blood was not altered materially. The cholesterol content of the blood showed marked but unexplainable fluctuations.

PROTOCOLS

CASE 1.—H. H., a married woman aged 50, in whom the menopause started at the age of 46, in May 1933 began to feel that something was wrong with her physically; no amount of medical reassurance to the contrary changed her mind. She knew that something was wrong with her abdominal organs and became depressed about it; she was worried and agitated and walked up and down, wring-

ing her hands and repeating over and over: "What brought this on? Why have I let myself slip?" She feared that her children were ill or injured and that her family was in trouble. She became self-accusatory, stating that she had done wrong. Her self-accusations and agitation became much worse, and she began to pull her hair, rub her hands and mumble, shout and scream. During and after treatment with theelin, no change was shown in the psychosis.

Case 2.—P. McM., a man aged 58, divorced, in 1932 began to feel profoundly depressed, for no definite reason. He questioned his sanity, complained of a feeling of tension inside his head and feared that a preexisting syphilitic infection was going to recur. This fear became so intense that he begged again and again for reassurance. He became agitated and restless and very nervous and shaky. He feared he would kill himself and expressed his fears over and over. He felt he was "no good" and finally was certain he was going to die, asking every one if it was not so. He then quieted somewhat, but recurrence of the same material occurred. He knew that he was going insane and that he would never get well. This type of material has continued. During and after treatment with theelin, he showed no changes that had not previously been experienced.

Case 3.—D. R., a married woman aged 44, in whom the menopause started at 40, during the early months of 1935 began to complain a great deal about her health, and particularly about a fear that she would acquire an incurable disease, such as cancer. She began to worry, became restless, agitated and anxious, paced back and forth and could not be quieted. She cried out over and over that the lining of her stomach "was burned out" and that she had "diseased lungs." She became profoundly depressed, wandered restlessly about, opened and closed windows and removed her clothes. She was self-accusatory and felt that she did not do right by her husband. She became more agitated, wringing her hands, tearing her clothes and saying over and over: "I was marked from my birth. I was destined for this." During and after treatment with theelin, no alterations in the mental or physical condition were noted.

Case 4.—G. N., a married man aged 42, in 1935 became nervous, depressed and disturbed. He felt that he had deserted his church and feared that war in Europe would kill his parents, who were there. He knew that something was going to happen to him; he feared that he would die and cried frequently. He became anxious, restless and agitated, and there developed a marked tremor of the head and hands. Then he knew something was going to happen to his wife. He repeated over and over: "I want to be a man again," and said that he was unworthy of his wife. His agitation became worse; he paced up and down, crying frequently, and refused to eat because he was unworthy of the food. He was given theelin. After a month he began to lose weight, in spite of feeding with a tube, and was unable to pass urine so that he had to be catheterized. There developed also marked and uncontrollable diarrhea. The mental condition became much worse and did not change after the treatment was completed.

Case 5.—A. C., a single woman aged 41, in whom the menopause started at the age of 37, in 1932 arose one morning and stated that she was going to church instead of to work. She started and then decided that she had better go to the police. Suddenly, she began to cry and admitted that she had not been eating or sleeping well. She became markedly depressed and disturbed and then threatened suicide. She became quieter for a short period, and then began to pace, rubbed her hands, was anxious and agitated and thought she was being watched and annoyed. She repeated over and over: "I am an operator; I want to go home to my mother," or "Get me my coat; I want to go home. Can I go home?" She thought that she was "going crazy," that she was being punished and that she

was responsible for the death of a child. She became threatening at times and more disturbed, restless, tense, agitated and depressed; she paced more constantly. She felt she should not be in a hospital, for she could not afford treatment, and that she should not sit on chairs she could not pay for. She was given theelin but showed no change in her mental or physical condition.

CASE 6.—T. L., a single man aged 38, in 1933 became tense, nervous and apprehensive and felt that mentally he was unable to succeed in his work. He had a fear that he would fail. He became depressed and could not eat or sleep well. He complained of nausea and trouble with his stomach. He thought that everything that was done for him was for the purpose of torturing him—of making him unhappy. He thought that he was to be killed, that his manhood was impaired, that he was a burden on others and that he had a "terrible disease." For periods he seemed somewhat better, but for only a short time, and then reverted to the state of apprehension, agitation, tenseness, fear and self-condemnation. He felt he would never get well. He was given theelin and during the treatment became worse. After the treatment had been completed, he reverted to his original mental state.

CASE 7.—B. C., a single woman aged 58, in whom the menopause started at the age of 45, was apparently well until she had panhysterectomy and bilateral oophorectomy, in 1933. Five weeks after the operation she began to express many somatic complaints. She could not sleep; she would not eat, for she knew her bowels were "no good." She thought no one cared for her and became depressed. She felt that she was going to die. Her "feelings" were gone from her, and she knew that she would never get well. She became agitated, restless and noisy. She wrung her hands, begged that something be done and expressed ideas of impending doom. She was treated with theelin but showed no change in the mental or physical condition during or after treatment.

CASE 8.—T. D., a single man aged 54, in 1934 gradually became depressed, unhappy and despondent. He moped, had no appetite and could not sleep. He became tense and agitated and suddenly attempted to cut his throat. He then stated that he was miserable, that life was not worth living, that he had committed "the unpardonable sin" and that he had been banned from his church. He became extremely agitated; he whined, picked at his skin, tore up pieces of paper and paced. He was markedly despondent because he felt that he had no "insides" and that he would die. He was treated with theelin. As the treatment progressed, he became physically and mentally worse; he lost weight and failed rapidly. Six months later he died.

CASE 9.—G. D., a single woman aged 51, in whom the menopause occurred at the age of 47, in 1932 appeared nervous and complained of pain in the back of her head. She became depressed and restless and whined and begged like a child for something to be done. She bewailed her state. She became worse and more depressed and said over and over: "Why don't you find my clothes?" or "How did this happen?" She expressed ideas of unworthiness and unreality. She screamed: "They are killing me," or "I am a heathen." She walked slowly back and forth and was depressed, agitated, tense, self-accusatory and nihilistic. She was treated with theelin but showed no mental or physical change during or after the treatment.

CASE 10.—I. McM., a single woman aged 44, in whom the menopause started at the age of 42, in November 1933 became worried and depressed. She could not sleep. This state continued until April 1934, when she suddenly began to pull at her dress and rub her face. She could not concentrate and was too restless to

read. She felt that she was not wanted, that she was going to be killed, that her kidneys were poisoning her, that "something had broken inside her," and that she was filled with pus. She knew that her bowels would not move nor her kidneys function. She became more anxious, restless and agitated. She paced back and forth, wringing her hands, pulling her handkerchief and muttering over and over: "I am a good, Christian woman; I am a good, clean woman." She received treatment with theelin and about one month after it was started began to have regular monthly periods. There has been no change in the mental condition and no other change in the physical state.

COMMENT

The results of treatment with theelin in cases of involutional melancholia presented in this paper are not encouraging—if anything, they are discouraging, for there was no instance of improvement or recovery in the group, whereas 70 per cent of patients remained unchanged and 30 per cent became definitely worse. In the group used as a control, on the other hand, the incidence of improvement (recovery) was 20 per cent.

These results are unlike those obtained by Werner, and it is difficult to reconcile such diametrically opposed findings. To the best of our clinical and laboratory knowledge, there was no evidence in our cases of cerebral arteriosclerosis or schizophrenia—or, for that matter, of any type of pathologic condition other than that of involutional psychosis. This may, of course, be verified by study of the protocols. Thus, it is evident that the failure to effect improvement in our cases can be explained only on the basis of the lack of therapeutic value of theelin for the psychoses treated.

On the other hand, Werner, who has presented such overwhelming evidence of the specificity of theelin as a therapeutic agent in involutional melancholia, expressed the belief that "theelin is curative in cases of uncomplicated involutional melancholia, [that] theelin accelerates recovery and shortens the period of mental illness or involutional melancholia [and that] the administration of theelin may be used as a therapeutic diagnostic test to differentiate between involutional melancholia and other types of mental disease occurring at the menopause." Unfortunately, he published no protocols of his cases to establish the diagnoses of what he referred to as "so-called involutional melancholia" —although he was willing to concede it as an entity when the theelin acted as a differential diagnostic agent. Again, when the theelin failed to obtain results, he explained his failures by calling the condition schizophrenia (certainly, this should have been recognized before the theelin failed to work) or by stating that the patients (still living) had cerebral sclerosis. (A diagnosis such as this cannot be made with any degree of accuracy in a living person; if he meant cerebral arteriosclerosis, it would appear that this pathologic condition could have been guessed with a fair degree of accuracy before treatment was started;

no one expects improvement in the real deterioration of cerebral arteriosclerosis.) In addition to this, Werner further explained his failures by such statements as: "evidence of mental retardation at the age of 5" (the psychosis developed at the age of 50) and "the patient had an aunt and an uncle who were mentally ill" or "a sister who had a mental disease and a cousin who was feebleminded." It would not appear that any of this random information could bear any definite relationship to the reasons that theelin did not work, "as yet."

It may be argued that we did not treat our patients for as long a period or with as much theelin as Werner and that this may explain our total of failures, as compared with his successes. That may be true, but it seems reasonable that if improvements were to be obtained, they would at least begin to manifest themselves in two and one-half months. Werner gave his patients 50 rat units of theelin daily for six months, or a total of 8,400 rat units. We gave our patients 300 rat units three times a week for ten weeks, or a total of 9,000 rat units; we therefore gave our patients more theelin than Werner. Again, it may be argued that we gave too much theelin in too short a time. That may be so, but even Werner has stated that it is his belief that with larger doses of theelin the rate of recovery would be increased.

The results that we have obtained from the use of theelin as a therapeutic agent in involutional melancholia make it impossible for us to recommend it as a therapeutic agent in this psychosis. In our hands theelin has been of no value; indeed, the mental condition in three of the cases definitely became aggravated, and in these three cases the physical condition likewise became more grave while the treatment was in progress. Whether this was coincidental or due to the theelin specifically cannot be said. In one of our cases, it is true, menstruation was regularly and, to date, consistently reestablished, but this has not improved the mental state. Just what advantage has been incurred by reestablishing the menstrual periods of this woman is uncertain to us. The Council on Pharmacy and Chemistry of the American Medical Association, in their report on estrogenic substances,[9] were likewise at a loss to explain what advantages are to be incurred in similar instances. They further expressed uncertainty as to the specificity of theelin in the treatment of psychoses of the involutional period of life. In addition, they stated that they were not sure but that theelin, if administered ad libitum might do harm. They called attention to the work of Kunde and her co-workers and to that of Haupstein in which "the daily injection into immature dogs of from 25 to 800 rat units for six to seventeen weeks resulted in relatively sclerotic ovaries less than one-

9. Estrogenic Substances: Theelin, report of Council on Pharmacy and Chemistry, J. A. M. A. **100**:1331-1338 (April 29) 1933.

half the size of those in control dogs, anterior hypophyses much smaller, and posterior hypophyses much larger than normal, and markedly hyperplastic thyroid together with other changes of a less serious nature." We have often wondered if any of these pathologic changes could have occurred in any or all of the three patients in our series who became worse while being treated with theelin.

It is fully recognized that the number of cases that we present is small. However, it is about as large as the group reported on by Werner in his first paper. As our results were consistently negative, results which are diametrically opposed to those reported in the existing literature, we felt it incumbent on us to report them. There may be cases of involutional melancholia in which theelin is of therapeutic value; we would not deny this. But there are also cases of this psychosis in which recovery or remission occurs spontaneously without theelin. The type which we treated, as judged by the severity of symptoms, was not, we believed, of this caliber. It was the type in which recovery does not depend on time or nonspecific therapy—the type which we judged would remain involutional melancholia indefinitely unless some specific therapy were found to interrupt such a course and return the patient to a normal mental state. It is in cases of this type that we have found theelin to be of no value.

SUMMARY

Theelin was administered to ten persons with involutional melancholia. In these ten patients there was no improvement or recovery. The condition of seven patients remained unchanged; in three the psychosis was aggravated during the treatment, and the physical condition became more grave.

Theelin was of no value in treatment in the cases of involutional melancholia studied.

EFFECT OF ROENTGENOTHERAPY ON GLIOMAS

I. M. TARLOV, M.D.*
NEW YORK

While there are a number of reports dealing with the effect of irradiation on patients with tumor of the brain, few studies of the histologic changes so produced have been made. Alpers and Pancoast [1] studied a series of twenty-two cases of glioma in which specimens were available before and after treatment. Like Bailey,[2] they found medulloblastoma to be sensitive to roentgen rays. Alpers and Pancoast reported changes in ependymoma following roentgen irradiation (increase in connective tissue stroma, thickening of the blood vessels and increase in necrosis). No appreciable change was observed in oligodendroglioma, astrocytoma or glioblastoma. Brody and German [3] concluded that fibrosis follows roentgenotherapy in cases of medulloblastoma. Deery [4] reported a study of fifty cases of glioma in which preirradiation and postirradiation specimens were available. Some of the tumors of each of the three types (medulloblastoma, glioblastoma and astrocytoma), constituting most of the series, showed "striking histopathologic changes which it seemed reasonable to credit to the radiation received. Other tumors showed less convincing changes while still others showed none."

The object of this study is to record the results of roentgen ray therapy on the microscopic appearance of a small series of gliomas. One must recognize the difficulty in evaluating the effect of roentgen rays on the clinical course in patients with this tumor. The exact size and site of the tumor, together with the extent of the operative removal, must be considered in this respect. Nevertheless, follow-up statements have been included in the table, in order to make possible some degree of correlation with the histologic change and the dose of roentgen rays.

From the Neurological Service of Dr. Ernest Sachs, the Barnes Hospital.

*Fellow in Neurological Surgery, the Washington University School of Medicine, St. Louis, 1935 and 1936.

1. Alpers, B., and Pancoast, H.: The Effect of Irradiation on Normal and Neoplastic Brain Tissue, Am. J. Cancer **17**:7, 1933.

2. Bailey, P.: Further Notes on the Cerebellar Medulloblastomas: The Effect of Roentgen Radiation, Am. J. Path. **6**:125, 1930.

3. Brody, B., and German, W.: Medulloblastoma of the Cerebellum: A Report of Fifteen Cases, Yale J. Biol. & Med. **6**:19, 1933.

4. Deery, E.: Remarks on the Effects of Roentgen Therapy upon the Gliomas, Bull. Neurol. Inst. New York **4**:572, 1936.

The material was obtained at operation before roentgen treatment and again, after irradiation, at a second operation or at autopsy. The handicaps inherent in such an approach are immediately evident, especially in such a tumor as glioblastoma multiforme, in which the structure may vary considerably in different portions of the growth. Operative specimens are sometimes small in relation to the extent of the tumor and are therefore not truly representative. However, the material is the best available for study at this time, and the results are presented for comparison with those from other clinics. It is only by careful scrutiny of the results in a large series of cases that one may hope for a better understanding of the effect exerted by roentgen rays on the biologic activity of glioma.

Before interpreting the change following irradiation, comparisons of changes observed in nonirradiated tumors of similar types were made. These untreated tumors served as controls, although they were not altogether adequate, since again examination was restricted to operative specimens. However, they served as a sort of standard, on the basis of which the changes produced by roentgen rays could be better evaluated.

TECHNIC OF IRRADIATION

The technic of irradiation has varied considerably during the time in which the patients whose records are included in this report were treated. In a few of the earliest cases irradiation was done with voltages ranging from 150 to 180 kilovolts (peak). In 1922 a 200 kilovolt roentgen ray machine was installed, and since 1931 a constant potential apparatus of that voltage has been employed. For the most part, the filter consisted of 1 mm. of copper and 1 mm. of aluminum, but in some of the recent cases only 0.5 mm. of copper was used. The target skin distance was 50 cm. in every instance. The size of the skin field varied from 50 to 400 sq. cm. From two to four irradiated areas were employed, with the beam directed toward the tumor-bearing region in each instance. Doses were recorded in terms of roentgens with back-scattering, but since July 1935 amounts of radiation have been expressed in terms of roentgens measured in air.

Owing to the complex variations in the treatment of these patients, certain liberties have been taken for the sake of simplicity in tabulating doses. An attempt was made to translate doses recorded in terms of roentgens with back-scattering into terms of roentgens in air. Estimations of roentgens in air were made from data presented by Quimby, Lucas, Arneson and MacComb.[5] Treatment was usually administered in single exposures of from 400 to 600 roentgens (in air) to each area. That amount was sometimes repeated in six weeks, further treatment depending on the clinical course. More recently, some of the patients have been treated by a technic of divided doses, requiring about two weeks. During that time from 1,000 to 1,500 roentgens was delivered to each area.

Measurements were made on several patients to determine the average fronto-occipital and biparietal diameters of children and adults. An average depth was also taken for tumors located in various portions of the brain. From these data

5. Quimby, E.; Lucas, C.; Arneson, A., and MacComb, W.: A Study of Back-Scatter for Several Qualities of Roentgen Rays, Radiology **23**:743, 1934.

the amount of radiation reaching the tumor was estimated for each patient and expressed in terms of "threshold doses."[6] For example, if a tumor located in the right half of the brain receives 75 per cent of the dose delivered to the right parietal region and 25 per cent of that delivered to the left side of the head, the total amount reaching the tumor will be 100 per cent. That value is relative to the amount delivered to one field. That is, if one threshold dose is administered to each area, the tumor will receive three fourths of a threshold dose from the treatment given to the right side of the head and one-fourth from the amount delivered to the left side. After total treatment is given, regardless of elapsed time, the tumor will have received one threshold dose. It should be noted that the estimation of the tissue dose is only approximate. If the values given are within 50 per cent of the actual amount of radiation arriving at the tumor, the data will serve the intended purpose as a basis for correlating the tumor dose with the histologic change.

In the table are given, for each patient, the number of irriadiated areas and the total dose delivered to each field. In every instance the percentage depth dose has been calculated, and from these data the tumor dose has been estimated in terms of the threshold dose. The values given are for all the treatment each patient received. The number of courses (or cycles) of roentgen irradiation, as well as the total period over which full treatment was administered, is given in the table. It has already been stated that approximately six weeks intervened between each series of treatments. The administration of a single course of treatment required from two to fourteen days.

MEDULLOBLASTOMA

The medulloblastomas presented striking histologic changes after irradiation (fig. 1 *A* and *B*). A decrease in the number of cells in the tumor, following degenerative changes in the cells, and an increase of connective tissue occurred. These changes were particularly well illustrated in V. S., S. R. and G. S. There were large areas in which tumor cells were almost completely replaced by fibrous tissue. Much of the fibrosis was composed of heavy collagen fibers, among which sometimes occurred groups of tumor cells, frequently pyknotic or shrunken. Occasional fat-filled monocytes occurred, but the number of phagocytes encountered was less than one would expect, considering the extent of pyknotic change in the tumor cells. Other portions of the tumor were quite as cellular as originally. In these regions true mitotic figures were sometimes encountered. They differed from the hyperchromatic and fragmenting nuclei seen in degenerating areas. Adventitial

6. The threshold skin dose is that quantity of radiation which, delivered in one exposure, at the rate of from 40 to 60 roentgens per minute, produces in 80 per cent of all patients a visible pigmentation within one month and in the others no visible reaction (MacComb, W., and Quimby, E.: The Rate of Recovery of Human Skin from the Effects of Hard or Soft Roentgen Rays or Gamma Rays, Radiology **27**:196, 1936). For 200 kilovolt roentgen rays filtered with 0.5 mm. of copper, with a field measuring 10 by 10 cm. on the skin of the forearm, the threshold dose is 525 roentgens (in air).

Initials, Age and Tumor Site	Duration of Symptoms Before Operation	Number of Cycles of Treatment	Time During Which Treatment Was Administered*	Number of Irradiated Areas	Dose Delivered to Each Area, in Roentgens (Surface Dose)	Approximate Total Amount of Radiation Reaching Tumor Bed, in Terms of Threshold Dose	Interval from Last Irradiation to Time at Which Specimen Was Obtained	Chief Respects in Which Postirradiation Specimen Differs from Preirradiation Specimen	Clinical Course	Evidence of Histologic Regression
Medulloblastoma										
1. V. S., 16 Cerebellum	12 months	3	9 months	2	1,000	2.0—	2 months	1. Less cellular 2. Pyknosis of cells 3. Great increase in connective tissue stroma	Death 12½ months after first operation	Definite
2. S. R., 6 Cerebellum	1-3 years	4	5 months	2	2,200	3.5+	3 weeks	1. Less cellular 2. Pyknosis of cells 3. Great increase in connective tissue stroma	Death 6 months after first operation	Definite
3. B. P., 10 Cerebellum	9 months	2	2 months	2	800	1.5+	7 weeks	1. Slightly less cellular 2. Increase in size of cells 3. Multinucleated cells 4. Moderate increase in connective tissue stroma	Death 3½ months after first operation	Definite
4. C. P., 16 Cerebellum	7 months	5	25 months	3	1,200	2.5—	3 months	1. Less cellular 2. Great increase in connective tissue stroma	Death 28 months after first operation	Definite
5. G. S., 1 Cerebellum	.....	2	1½ months	2	900	2.0	3 months	1. Less cellular 2. Pyknosis of cells 3. Great increase in connective tissue stroma 4. Differentiation of cells toward ganglion cells and neuroglia	Death 5 months after first operation	Definite
6. J. L., 28 Cerebellum	6 months	8	24 months	4	2,400	9.0	3 months	1. Pyknosis of cells 2. Moderate increase in connective tissue stroma	Somewhat improved 29 months after first operation (additional 4,000 roentgens delivered through open wound 28 months after first operation)	Definite
Glioblastoma multiforme										
7. M. R., 33 Right temporal	8 months	2	1½ months	2	1,200	2.0—	1 month	1. Increase in necrosis with beginning of connective tissue repair	Improved 17 months after first operation (radon seeds implanted 3 months after first operation)	Slight
8. H. W., 24 Right parieto-temporal	2 months	1	2 days	2	450	1.0—	14 months	1. Increase in number of swollen cells (astrocytes and spongioblasts) 2. Increase in number of multinucleated giant cells	Death 21 months after first operation	Absent
9. F. M., 43 Left frontal	2 months	4	6 months	2	1,000	2.0—	22 months	1. Increase in number of swollen cells (astrocytes and spongioblasts) 2. Slight hyaline degeneration of blood vessels with hemorrhage	Death 36 months after first operation	Absent
10. J. L., 43	6 months	3	3 months	3	1,000	2.0—	4 months	1. Increase in focal necroses	Death 11½ months after	Slight

10. J. L., 43 Left occipital	6 months	3	3 months	2	1,000	2.0—	4 months	1. Increase in focal necroses 2. Slight fatty degeneration of blood vessels 3. Slight increase in connective tissue	Death 11½ months after first operation (radon seeds implanted 6 months after first operation)	Slight
11. J. P., 47 Right temporal	9 months	2	9 months	2	500	1.0—	7 months	1. Increase in number of swollen cells (astrocytes and spongioblasts) 2. Decrease in connective tissue	Death 17 months after first operation (additional 1,248 roentgens before death)	Absent
12. J. A., 56 Left parietal	9 months	4	8 months	2	1,200	2.0	2 weeks	1. Increase in focal necrosis 2. Slight fatty and hyaline degeneration of blood vessels	Death 13 months after first operation	Absent
13. C. B., 39 Right temporal	4 months	2	2 months	3	1,200	3.0	2 months	1. Extensive cystic degeneration and some focal necrosis 2. Great increase in connective tissue 3. Increase in multinucleated giant cells	Death 6 months after first operation, from pneumonia	Fairly definite
14. M. B., 26 Left frontal	18 months	1	9 days	3	600	2.0—	1½ months	1. Slight increase in necrosis	Unimproved 6 months after first operation (radon seeds implanted 2 months after first tumor removal)	Absent
Medulloepithelioma										
15. A. M., 11 Corpus callosum	12 months	2	1½ months	2	1,000	1.5+	1 month	1. Moderate increase in connective tissue stroma	Death 25 months after first operation	Slight
Astroblastoma										
16. R. J., 16 Right parietal	3 months	4	5 months	2	1,000	1.5+	2½ weeks	1. Increase in necrosis 2. Great variation in size and shape of cells 3. Many multinucleated giant cells 4. Slight increase in connective tissue stroma	Death 9 months after first operation	Slight
17. A. V., 24 Right temporal	6 months	2	3 months	2	450	1.0—	1¾ months	1. Increase in necrosis 2. Great variation in size and shape of cells 3. Many multinucleated giant cells 4. Greater differentiation toward astrocytes in one area 5. Slight increase in connective tissue stroma	Death 4 months after first operation	Slight
Astrocytoma										
18. B. G., 36 Right frontal	12 months	3	12 months	2	1,700	3.0—	1 week	1. Moderate increase in number of multinucleated giant cells 2. Moderate increase in number of capillaries 3. Slight increase in number of mitoses	Death 14 months after first operation (meningitis)	Absent
19. R. E., 6 Cerebellum	3 months	3	4 months	2	500	1.0—	3 months	1. Slight increase in neuroglia fiber stroma	Death 7 months after first operation	Absent
20. L. G., 5 Cerebellum	6 months	5	42 months	2	700	1.5—	37 months	1. Slight increase in neuroglia fiber stroma 2. Slightly more cellular	Fairly well 84 months after first operation (total of 5,250 roentgens received up to the time of writing)	Absent

* The approximate time interval between preirradiation and postirradiation specimens is represented by the time during which the treatment was administered plus the interval from the last irradiation to the time at which the postirradiation specimen was obtained plus an additional two weeks which represents the period elapsing usually between operation and the beginning of irradiation.

Initials, Age and Tumor Site	Duration of Symptoms Before Operation	Number of Cycles of Treatment	Time During Which Treatment Was Administered*	Number of Irradiated Areas	Dose Delivered to Each Area, in Roentgens (Surface Dose)	Approximate Total Amount of Radiation Reaching Tumor Bed, in Terms of Threshold Dose	Interval from Last Irradiation to Time at Which Specimen Was Obtained	Chief Respects in Which Postirradiation Specimen Differs from Preirradiation Specimen	Clinical Course	Evidence of Histologic Regression
21. M. G., 31 Right frontal	22 months	1	2 days	2	400	1.0—	7 months	1. No change	Death 71 months after first operation	Absent
							Second postirradiation specimen			
							70 months	1. Slightly more cellular in certain areas		
22. M. N., 21 Cerebellum	2 years	2	4 months	2	700	1.0+	21 months	1. No change	Improved 102 months after first operation	Absent
23. J. P.,† 21 Left cerebral	3 months	2	6 months	4	2,600	10.0	2½ months	1. Degenerative changes in cells of tumor and in blood vessels 2. Degenerative changes in adjacent brain 3. Moderate necrosis with connective tissue scarring 4. Widespread growth of tumor throughout brain 5. Subarachnoid spinal tumor implant 6. Lower level of cell differentiation	Death 9 months after first operation	Definite in certain areas; evidence of increased activity in other areas
Ependymoma										
24. C. S., 9 Right frontal	8 months	1	3 days	2	450	1.0—	4 months	1. Greater variation in size of nuclei 2. Moderate numbers of multinucleated cells 3. Cystic degeneration of tumor with slight increase in connective tissue stroma	Death 11 months after first operation	Slight
25. O. S.,‡ 37 Left temporal	6 months	6	20 months	2	2,000	4.0—	4 months	1. Moderate numbers of multinucleated cells		
							Second postirradiation specimen			
							3 weeks	1. Moderate numbers of multinucleated cells 2. Occasional mitosis 3. Slight increase in connective tissue stroma	Death 22 months after first operation	Absent
							Spinal tumor implant (third postirradiation specimen)			
							1½ months	1. Moderate increase in mitosis 2. Great increase in connective tissue stroma		
Oligodendroglioma										
26. M. B., 50 Left frontoparietal and corpus callosum	30 years	1	2 days	2	500	1.0—	23 months	1. Slight focal necroses 2. Occasional multinucleated cell 3. Slight vascular proliferation 4. Increase in number of astrocytes in certain areas	Death 25 months after first operation	Absent

* The approximate time interval between preirradiation and postirradiation specimens is represented by the time during which the treatment was administered plus the interval from the last irradiation to the time at which the postirradiation specimen was obtained plus an additional two weeks which represents the period elapsing usually between operation and the beginning of irradiation.

† The tumor in this case, although included with the astrocytomas because of the predominance of astrocytes, presented mitotic figures and numbers of immature cells.

‡ Approximately three times as much radiation was delivered to the tumor before the second specimen was obtained as before the third and the fourth specimen.

thickening was encountered in some postirradiation specimens, the fibrous stroma extending, however, much beyond the walls of the vessels. In case B. P. an increase in size of the cells with respect to both

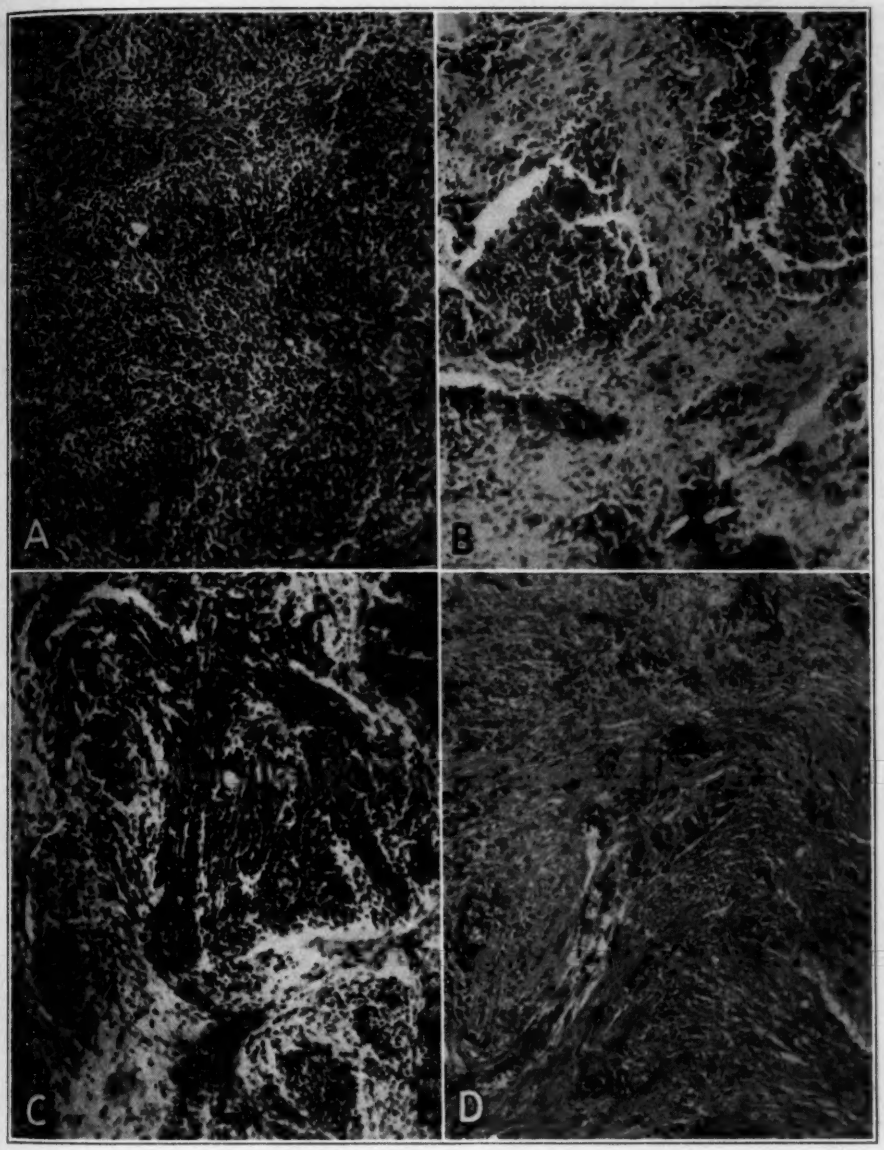


Fig. 1.—Medulloblastoma; hematoxylin and eosin × 100. *A*, preirradiation (V. S.); *B*, postirradiation specimen (V. S. 1), showing the great increase in connective tissue stroma and pyknosis of the tumor cells; *C*, preirradiation specimen (G. S.), and *D*, postirradiation specimen (G. S.), showing the extensive connective tissue stroma, with islands of ganglion cells and glia cells (*G*).

the nucleus and the cytoplasm followed roentgen therapy, the cytoplasm becoming strongly eosinophilic.

No strict correlation existed in these cases between the intensity of histologic changes following irradiation and the dosage of roentgen rays (table). Changes were not most marked in J. L., to whom the greatest amount of irradiation was administered. However, little tissue was available for examination in this case, since the tumor was removed chiefly by suction and the material thus removed was inadvertently discarded. In view of the patchy nature of the changes following irradiation, it is possible that the fragements of tumor examined represented cellular portions of the tumor. Much of the material removed by suction might have presented more marked degenerative changes with fibrosis. Among the other patients the changes were most marked in V. S., S. R. and C. P., who received the greatest roentgen doses. The changes were least marked in B. P., to whom the smallest dose was administered. However, in G. S. the changes were much more marked, although the dose of roentgen rays was little greater. This case is of particular interest. At autopsy a large tumor was seen filling the fourth ventricle. It measured about 7 cm. in diameter and was grayish and firm. The tumor presented compartments ranging from a few millimeters to 2 cm. in diameter, well outlined by glistening fibrous bands up to several centimeters in thickness. Microscopic study revealed pyknosis of tumor cells, with extensive replacement by collagen stroma. Furthermore, there was evidence of differentiation of many of the tumor cells toward polar cells, with more adult neuroglial forms and well formed ganglion cells (fig. 1 *C* and *D*).

The postoperative period of survival was longest for J. L., for whom the tumor dose was greatest. Of the remaining patients, the period of survival was longest for C. P., in whom the evidence of histologic regression was marked. However, it is readily seen that the period of survival in all cases does not parallel the intensity of irradiation or the extent of the histologic change.

Examination in a case of medulloblastoma used as a control, in which roentgen therapy was not administered, revealed a slight increase in connective tissue stroma in the second specimen, which was obtained three months after the first. Groups of pyknotic nuclei occurred in the second specimen, in which blood vessels were thickened. The fact that the amount of connective tissue and the extent of the pyknotic changes in all the postirradiation specimens greatly exceeded that in the case used as a control favors the conception that the changes resulted from roentgen rays.

GLIOBLASTOMA MULTIFORME

The tumors included in the category of glioblastoma multiforme conformed to the usual standards of classification—polymorphism of

cells, proliferative vascular change, necrosis and mitoses. An increase in the number of swollen cells, such as occurred frequently after irradiation, cannot be considered as evidence of change in the rate of growth, since these cells may represent either the more primitive (spongioblastic) or the more adult (astrocytic) cell types. There was a somewhat greater tendency to hemorrhage in a few cases in which degenerative vascular changes had occurred. However, this was not marked. Multinucleated cells and odd nuclear forms were commonly seen in increased numbers after irradiation. In M. R. slight histologic regression was suggested by the early cystic degeneration in one portion of the tumor, with incipient connective tissue scarring. In J. L. there was some increase in necrosis, with connective tissue scarring. However, in both cases the changes were within the range of variation seen in nonirradiated tumors. In C. B. there was more definite evidence of regressive change, with extensive cystic degeneration and connective tissue scarring (fig. 2). In the remaining five cases there was no convincing evidence of histologic regression, although an increase in necrosis occurred in two cases. In none of the cases could any definite change in the relative proportions of the more primitive and the more adult cell types be determined.

That not all the changes observed in the tumor after roentgenotherapy are attributable to the treatment is indicated by examination in three cases of glioblastoma in which no roentgen therapy had been administered. Specimens were obtained by operation at intervals of two and four months. In one case the second specimen differed from the first in presenting fewer mitoses, more necrosis and some connective tissue scarring. Such changes might ordinarily be construed as evidence of regression of the tumor resulting from irradiation. It is important to realize, therefore, that they may occur within the range of variation in a tumor at some stage during its lifetime. In the other two cases a considerable increase of swollen cells, together with multinucleated cells, occurred in the second specimen. In the first specimen in one of these cases odd nuclear figures, such as occurred in some postirradiation specimens, were fairly numerous. M. B. illustrates the importance of appreciating changes caused by operation in evaluating histologically the results of roentgen treatment. The first specimen from the tumor in this case was obtained one month after the initial operation, at which time the arm area on the same side was removed. Blood vessels in the brain at some distance from the tumor showed moderate connective tissue thickening. Similarly, due allowance must be made for a certain amount of connective tissue scarring extending from the meninges into the bed of the tumor, which usually follows operation.

In the control cases are indicated the hazards of attributing changes following irradiation to roentgen treatment, especially in a tumor of such variegated appearance as glioblastoma. The histologic changes in this group of tumors are unimpressive as indications of the tumor regression, with the possible exception of those noted in C. B. In this case there was extensive cystic degeneration, with fibroblasts streaming into the areas of necrosis, finally producing a dense connective tissue scar. These changes would constitute a desirable outcome were it not for the concomitant invasion of the brain by vigorous-looking tumor cells. The cases in this series are too few and the variables too great

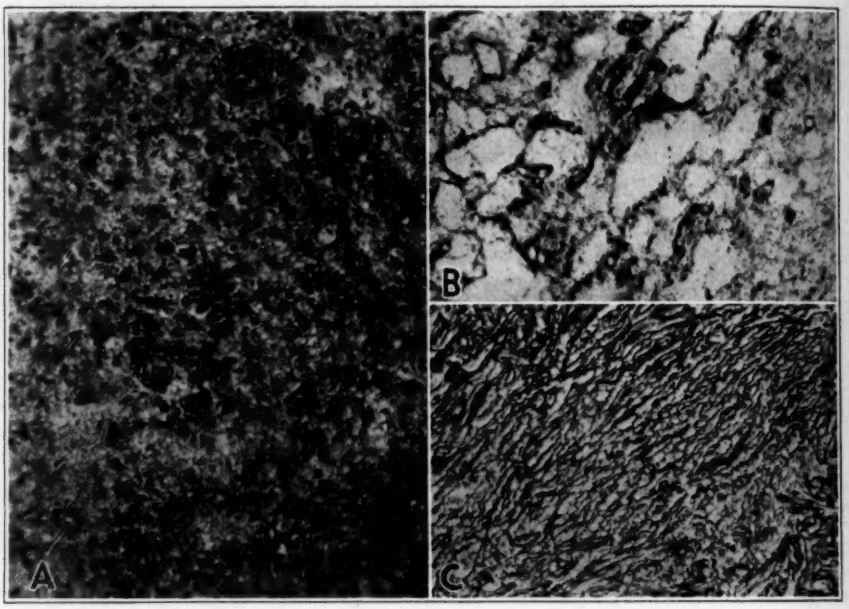


Fig. 2.—Glioblastoma multiforme (C. B.). *A*, preirradiation specimen (hematoxylin and eosin; × 100); *B*, postirradiation specimen, showing cystic degeneration (hematoxylin and eosin; × 31.5, and *C*, postirradiation specimen showing the collagen and reticulin of the extensive connective tissue scar (Perdrau's silver impregnation; × 100).

to permit deductions as to the relationship between the intensity of irradiation with histologic change and the period of survival. However, it is of interest that the evidence of histologic regression was most marked in C. B., who was given the greatest tumor dose of roentgen rays. This patient was much improved just before his death from pneumonia, six months after the first removal of tumor tissue.

MEDULLO-EPITHELIOMA

The single medullo-epithelioma observed was characteristic (fig. 3). The tumor might be included with the neuro-epitheliomas, although many of the cells appeared more embryonic than primitive spongioblasts. In spite of the numerous mitotic figures, calcification occurred in the original specimen. The postirradiation specimen presented more connective tissue than originally. Since little tissue comprised the preirradiation specimen, one cannot be certain that the change was not within the range of normal variation in structure of the tumor. How-

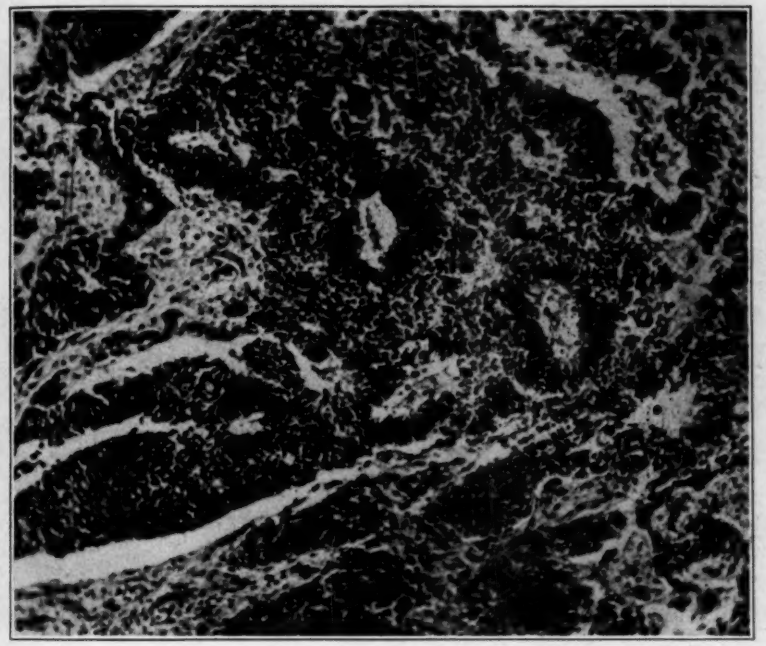


Fig. 3.—Medullo-epithelioma (A. M.). A slight increase in connective tissue stroma followed irradiation. Hematoxylin and eosin; × 100.

ever, on the basis of Ewing's [7] prediction that the least differentiated tumors should react most favorably to roentgen therapy, one would expect a high degree of sensitivity to roentgen rays on the part of the medullo-epithelioma.

ASTROBLASTOMA

In the two cases of astroblastoma well marked histologic changes occurred after irradiation. The postirradiation specimen of R. J.

7. Ewing, J.: Tumors of Nerve Tissue in Relation to Treatment by Radiation, Am. J. Roentgenol. **8**:497, 1921.

showed considerable variation in the size and shape of the cells. Many were multinucleated, and bizarre cell types with fragmentation of nuclei appeared (fig. 4). Focal and massive areas of necrosis were prominent, and the blood vessels presented adventitial thickening. Slight connective tissue scarring occurred in some areas. An operative specimen taken two months after the original one, during which interval no roentgen treatment had been given, served as a control. Slight changes occurred, but they were not of the extent encountered after irradiation. The change consisted of moderate increase in necrosis and some proliferation of adventitia and endothelium. Changes similar to those described

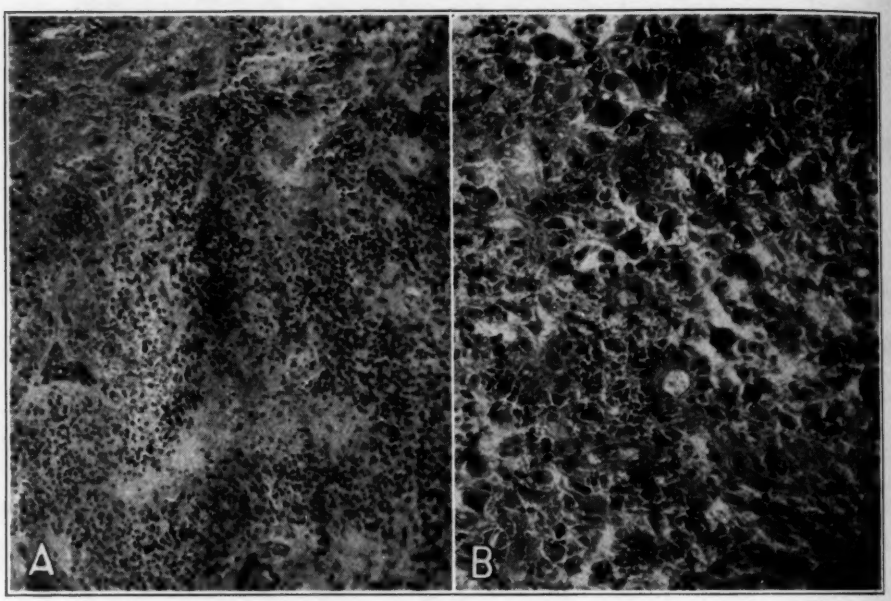


Fig. 4.—Astroblastoma (R. J.). *A*, preirradiation specimen, and *B*, postirradiation specimen, showing abundance of multinucleated giant cells. Hematoxylin and eosin; × 100.

in the aforementioned case occurred in one part of the postirradiation specimen of A. V. There were variability of cell forms, including multinucleated cells, and necrosis. Degenerating cells were abundant. In another portion of the tumor great numbers of small star-shaped astrocytes occurred, indicating the extent to which different areas of a tumor may vary. The features of cellular polymorphism and necrosis were so striking in these cases as to suggest the diagnosis of glioblastoma multiforme at first. However, further study indicated that the level of cell differentiation was not lower than that in the original tumor. Mitotic figures were not strikingly more prominent than orig-

inally, and the variability of cell type was probably the result of degeneration. The changes did not, therefore, indicate increased vigor of growth but, more likely, the reverse.

ASTROCYTOMA

In two of five cases of astrocytoma the sole histologic change following irradiation was a slight increase in neuroglial fiber stroma, the tumor being somewhat more cellular in one of these cases and in a third case; the tumor in all three cases was essentially of the fibrous type. These changes were observed in one of the two control cases in which the specimens were obtained fourteen months apart. In the second control case no change was presented in the two specimens. In B. G. the tumor tissue presented an increase in the number of multinucleated cells after irradiation, together with the appearance of a few mitotic figures. Degenerative changes were indicated by the occurrence of bizarre types of nuclei and cells, with endothelial swelling and fatty and hyaline degeneration of blood vessels. Many astrocytes of the plump cell type occurred in this specimen originally. No essential change occurred in a fifth case—an instance of fibrous astrocytoma of the frontal lobe.

The condition presented by J. P. merits more detailed consideration, since a large dose of roentgen rays was administered and subsequent changes were most marked. He was a 21 year old Negro laborer, who was admitted for investigation as to the cause of two attacks of unconsciousness. The attacks occurred one month and one week prior to his admission to the hospital and were accompanied by generalized convulsions. Several days after his admission to the hospital occurred a convulsive seizure, with conjugate deviation of the head and eyes to the left and without loss of consciousness. The family and the past history revealed no significant facts, except that the patient had had an occasional headache (about once a week) all his life. The only abnormalities on physical examination were absence of abdominal reflexes and inequality of the ankle jerks, the left being more active than the right. After encephalography the diagnosis of a tumor of the right frontal lobe was made. On March 25, 1935, a tumor weighing about 12 Gm. was removed from the arm area on the right side. No clearcut demarcation between the tumor and the brain existed. From April 2 to April 16 single daily exposures of 400 roentgens were given in succession to each of four skin fields (the right and left parietal, the occipital and the area just anterior to the vertex) until a total of 1,200 roentgens had been delivered to each area. Convalescence was uneventful, and the patient was discharged on April 17, at which time left hemiparesis of moderate severity was present. Since it was realized that the tumor had been incompletely removed, the roentgen treatment was repeated between June 18 and June 21, except that the beam directed to the left parietal region was omitted. The condition continued essentially unchanged until the early part of September 1935, when the hemiparesis increased and he began to use a cane to get around. A third cycle of irradiation was administered from September 30 to October 3, when a single exposure of 500 roentgens was delivered to each skin field.

Over a period of six months, then, the patient received a total dose of 2,900 roentgens to each of three fields and 1,700 roentgens to a fourth (left parietal). The dose delivered to the tumor-bearing region was estimated by Dr. Arneson to have been about 10 threshold erythema doses. After the last roentgen treatment walking became increasingly difficult. He was readmitted to the hospital on December 6, hiccups having occurred intermittently for several days prior to his admission. Three convulsive attacks had occurred between his admissions to the hospital, the first seizure being one month after discharge and the last four days before readmission. Consciousness was retained during these attacks. Physical examination at the time of readmission revealed slowness of all mental reactions and left hemiplegia, with impairment in appreciation of discriminatory sensation on the left. The decompression was flat and soft. Since the patient was left handed, an attempt to remove the tumor completely was considered advisable.

On December 16 a tumor weighing about 48 Gm. was excised from the left frontotemporal region, together with some of the surrounding brain. The patient recovered from the effects of the operation, but the mental dulness continued. It became increasingly difficult to understand his speech and to get him to swallow or to carry out commands. There followed complete apathy, with failure to talk, swallow or chew, and he died on Jan. 24, 1936.

Macroscopic Examination.—At autopsy the dura at the operative site was observed to be thickened and adherent to the margin of the cavity from which the tumor had been removed. The leptomeninges appeared slightly thickened. There were no surface nodules, and the cortex was smooth. The brain was sectioned coronally about every 0.75 cm. from the frontal to the occipital pole. The entire temporal lobe on the right side was replaced by tumor. The tumor involved grossly a portion of the adjacent frontal lobe anteriorly. It was gray and firm and presented a few yellowish streaks and an occasional hemorrhage, the largest about 1.5 cm. in diameter. The anterior half of the right side of the brain was diffusely enlarged to about twice the size of that on the left. There were a few small areas of softening within the white matter on both sides. The white matter throughout was rather firm. In a few areas of both frontal lobes the demarcation between the gray and the white matter was less clearcut than normally. Projecting from the superior and the medial wall of the right lateral ventricle at the approximate junction of the body and the frontal horn of the ventricle was a firm grayish nodule, about 1 cm. in diameter. On the lateral wall of the left ventricle there was some roughening of the ependyma, presenting flat, slightly raised areas. At first no abnormality of the basal ganglia, thalamus and pons was observed. However, microscopic studies of these areas revealed tumor, and reexamination of the gross specimens showed some obliteration of the normal markings of the various portions of these structures, which were firmer than normally. External examination of the spinal cord showed a nodule along its anterior aspect (fig. 6*D*). It extended from the upper lumbar region about 1.5 cm. caudally. On cut section the tumor was uniformly grayish. It involved the entire anterior aspect of the cord, extending to the meningeal surface. The substance of the cord was reduced to a cap 3 mm. thick at its posterior border, which tapered off on either side. The meninges of the entire cord were thickened and pearly gray in some areas. Blocks of tissue were taken of the entire brain and spinal cord. They were fixed in Zenker's solution in preparation for staining with hematoxylin and eosin, Mallory's phosphotungstic acid and Perdrau's connective tissue method; in a 10 per cent solution of formaldehyde, U. S. P., for staining with scarlet red and the Gros-Bielschowsky and the Weigert-Pal technics; in a solution of formaldehyde and

ammonium bromide for the metallic impregnation methods and in alcohol followed by embedding in pyroxylin for nerve cell stains.

Microscopic Examination.—Preirradiation Specimen: The tumor was uniformly cellular (fig. 5 *A*). The nuclei were round or oval, with moderate amounts of evenly distributed chromatin granules and delicate nuclear membranes.

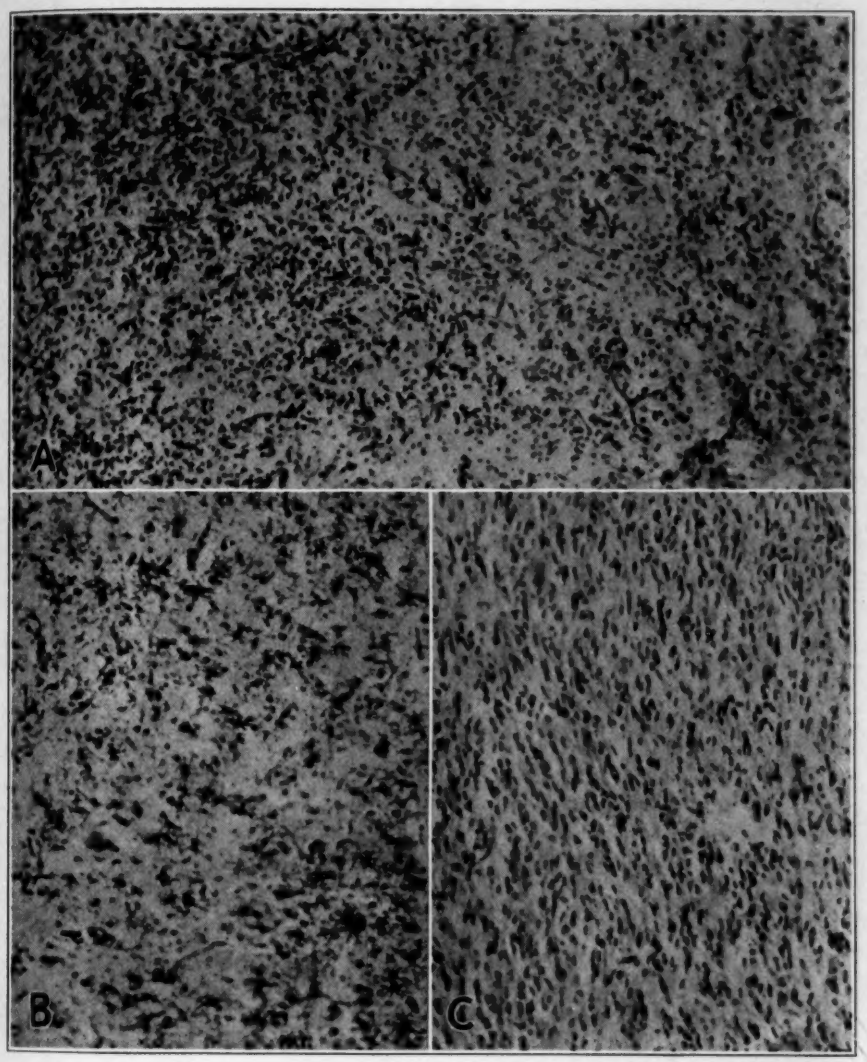


Fig. 5.—Astrocytoma (J. P. [case 23]). *A*, preirradiation specimen (hematoxylin and eosin; × 100); *B*, preirradiation specimen, showing numbers of astrocytes in the tumor (gold chloride-mercuric chloride impregnation; × 100), and *C*, postirradiation specimen (hematoxylin and eosin; × 100). Note the elongated cells, which are the predominant cell type (polar spongioblasts).

The cytoplasm was indefinite in preparations stained with hematoxylin and eosin, but in those stained with phosphotungstic acid numerous intracellular fibers could be seen. Gold chloride-mercuric bichloride preparations revealed many astrocytes (fig. 5 *B*). In addition, astroblasts occurred in a few areas, presenting the characteristic radiation around blood vessels. Blood vessels were numerous, and there was some vascular proliferation, chiefly adventitial. Connective tissue was limited entirely to the blood vessels. A few mitotic figures occurred.

The predominant cell type was the astrocyte. The occurrence of areas suggestive of astroblastoma, together with the presence of a few mitotic figures, favored the conception of the tumor as more rapidly growing than the usual astrocytoma.

Postirradiation Specimen: Part of the tumor suggested a very fibrous astrocytoma, although some areas presented numbers of less differentiated neuroglia cells. The most striking changes that had occurred were degenerative and proliferative. Blood vessels were much more numerous than originally. They were small, for the most part presenting adventitial thickening, extensive hyalinization and calcification (fig. 6 *A*). Numerous balls of calcification of varying size occurred. Many began as dots of calcification in the walls of vessels leading in some instances to complete vascular occlusion. Deposits of calcium in other instances were seen in relation to cells of the tumor or the adjacent brain. A few tumor astrocytes were of the Nissl plump cell type, and occasional multinucleated cells occurred. The perivascular spaces were frequently distended by lymphocytes or fat-filled phagocytes. Numerous young fibroblasts could be seen streaming out toward large areas filled with fat-laden cells. In some of these zones, located at some distance from the site of operation, an abundant reticulin stroma occurred. The tumor invaded the subarachnoid space and the adjacent brain.

The brain adjacent to the tumor had undergone well marked degenerative changes. Blood vessels were numerous, presenting thickening, hyalinization and calcification, with complete occlusion in some cases. The meninges were thickened and infiltrated by lymphocytes. Nerve cells presented evidence of chromatolysis, with satellitosis and neuronophagia (fig. 6 *C*). Hypertrophy and degeneration of astrocytes occurred. There were a few examples of moderate swelling of oligodendrocytes, but these changes were not impressive. Early changes in microglia cells toward rod cells were seen, and there were numerous fat-filled phagocytes in the brain around the tumor.

Specimen Removed at Autopsy: The tumor occurred chiefly at the anterior and the inferior border of the cavity. In this region the specimen was essentially of the same pattern as that removed at the second operation. A few areas of focal necrosis were present, and degenerative changes had occurred in the cells. Elsewhere around the cavity there was marked softening, with some hemorrhage. Nowhere in this region was the brain normal. There was widespread replacement of brain tissue by tumor. Involvement of the opposite cerebral hemisphere was so extensive that it was first believed that multiple tumors were present. Later it was possible to trace the spread of the tumor by direct extension from the right frontotemporal region through much of the centrum semiovale on this side to approximately the tip of the frontal lobe. The tumor extended along the corpus callosum, involving much of the centrum semiovale of the opposite side. The tumor occurred practically throughout the basal ganglia, thalamus and pons and extended along the brachium pontis into the white matter of the cerebellum. Weigert-Pal preparations revealed great numbers of myelinated fibers passing through the pons and the basal ganglia. Numerous inclusion ganglion cells in

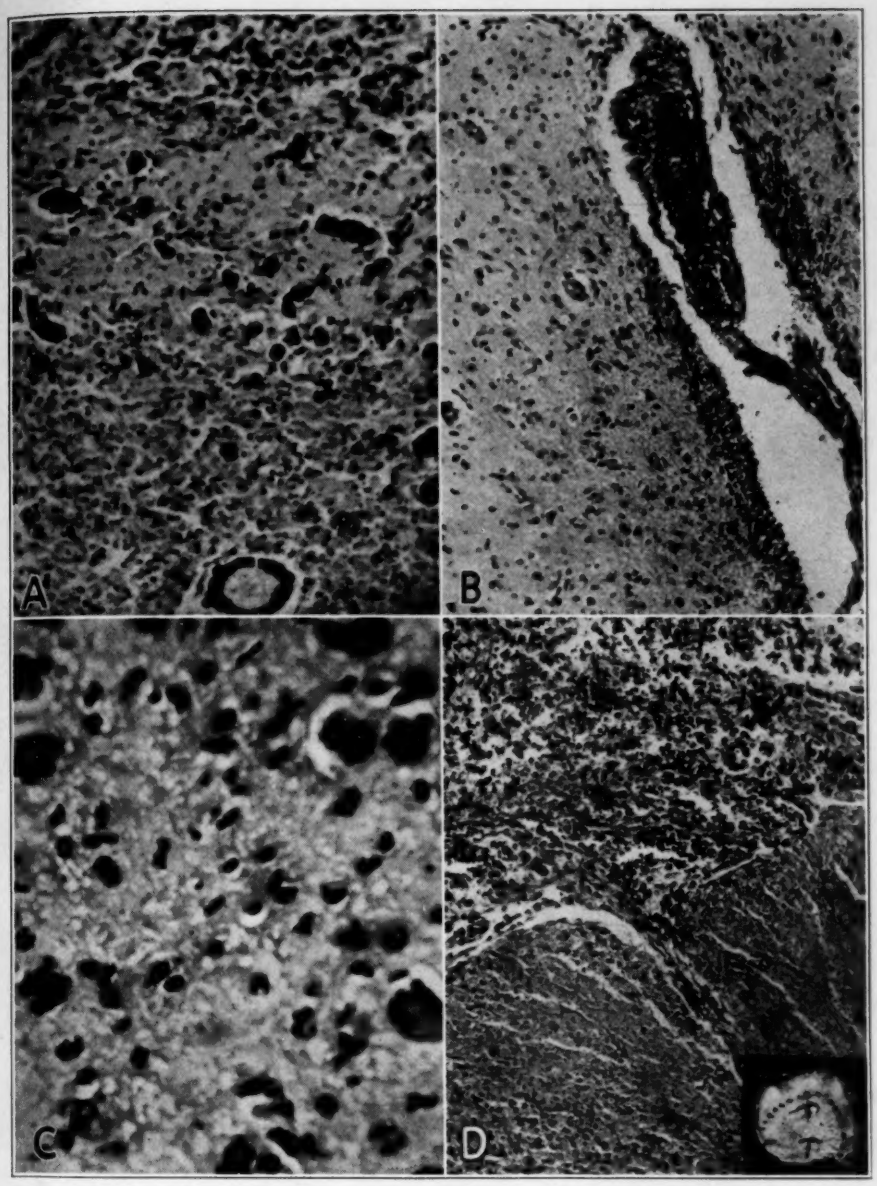


Fig. 6.—*A*, postirradiation specimen (J. P. [case 23]), showing extensive calcification and multinucleated giant cells. Hematoxylin and eosin; × 100. *B*, postirradiation specimen (J. P. [case 23]), showing replacement of normal marginal neuroglia by layers of cells resembling those of the tumor (spongioblasts and astrocytes) and extending along the pial septums. Note also the thickening of the blood vessels of the brain. Hematoxylin and eosin; × 100. *C*, brain tissue (J. P. [case 23]) adjacent to the tumor following irradiation, showing neuronophagia. Hematoxylin and eosin; × 370. *D*, tumor in the lumbar portion of the spinal cord (J. P. [case 23]). The predominant tumor cell is the spongioblast, many astrocytes occurring. Hematoxylin and eosin; × 100. The insert below on the right is a photograph of the gross specimen, showing invasion of the spinal cord by a tumor implant *T* (outlined by dotted lines).

varying stages of degeneration could be seen in the basal ganglia and in the regions of the frontal and temporal cortex where the tumor had invaded the gray matter. Marked satellitosis had occurred, clusters of satellite cells resembling tumor cells. Posteriorly the tumor did not extend beyond the level of junction of the body and the inferior horn of the lateral ventricle. Subpial tumor frequently replaced the marginal neuroglia and the superficial cortical cell layer (fig. 6*B*). The tumor cells frequently extended into the cerebral sulci and as cuffs along blood vessels. The tumor reached the subependymal zone and in several regions grew into the ventricle.

The pattern of the tumor varied markedly in different areas. Near the operative site the predominant type of cell was the astrocyte, although less differentiated polar cells occurred. In the pons and the basal ganglia the pattern was different; it was typically that of a polar spongioblastoma (fig. 5*C*). Calcification occurred in this area, but less commonly than elsewhere. In the subependymal region and the ventricular nodules the pattern was still different. The cells were more uniformly round, their nuclei containing considerable chromatin, usually surrounded by a small amount of ill defined cytoplasm. Short processes could frequently be seen projecting from these cells. It seemed that the predominating type of cell in these areas was a primitive spongioblast. The transition between the various patterns of tumor was gradual. The most striking change in the uninvaded area of the brain and the spinal cord pertained to the blood vessels. Considerable connective tissue thickening of their walls had occurred—more than is ordinarily seen after operation.

Microscopic examination of the nodule in the upper lumbar region showed a cellular tumor similar in structure to portions of the tumor in the brain. Its cells were round or elongated, with short projections representing spongioblasts and astrocytes, predominantly the former. Occasional multinucleated giant cells and mitotic figures occurred. Elsewhere too in the subarachnoid space tumor cells occurred, chiefly anteriorly and growing along the median fissure. The tumor extended outward a short way among the bundles of nerve roots.

Microscopic examination of the various organs removed at autopsy revealed no significant abnormalities.

Summary.—The following features were of interest in the specimen after irradiation: (1) the occurrence of degenerative changes in the tumor, with the formation of a connective tissue scar, (2) the marked proliferation and degeneration of blood vessels in and around the tumor, (3) the degeneration of ganglion cells around the tumor, (4) the widespread infiltration of much of the entire brain by tumor and (5) the occurrence of subarachnoid tumor implants in the spinal cord. These features will be commented on later.

EPENDYMOMA

The degenerative changes with fibroblastic proliferation and multinucleated cells occurring in the postirradiation specimen in C. S. (case 24) were not encountered to such a degree in the control case. In the other case of ependymoma the opportunity was presented of examining the tumor after three successive courses of irradiation. After the first course the specimen presented an increase in the number of multinucleated cells. These cells differed from those commonly encountered in glioblastoma multiforme in that they were smaller, the nuclei

were less bizarre and the cytoplasm was less voluminous. The second postirradiation specimen contained a few mitotic figures and a slight increase in connective tissue stroma, with thickening of blood vessels. The third postirradiation specimen, curiously, was obtained at operation from the cervical portion of the spinal cord. It was about the size of a large pea and lay anteriorly at the level of the third spinal segment, being extramedullary and intradural. This specimen consisted of islands of ependymal cells within an extensive cellular connective tissue stroma (fig. 7). The blood vessels were moderate in number and of normal appearance.

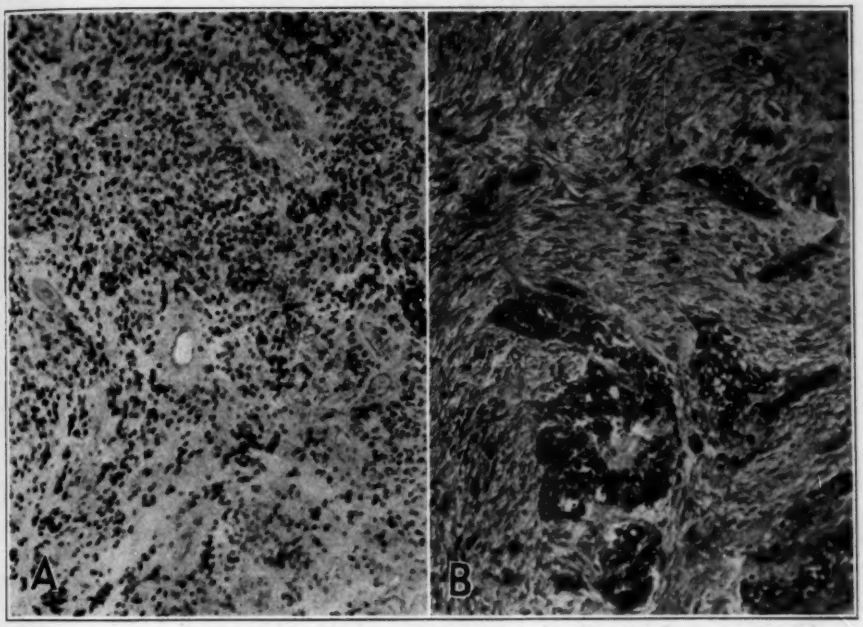


Fig. 7.—*A*, preirradiation section from an ependymoma of the temporal region (C. S. [case 25]) and *B*, postirradiation section from a subarachnoid spinal (cervical) implant of ependymoma (C. S. [case 25]). Numerous mitoses occur. Note the abundance of connective tissue stroma. Hematoxylin and eosin; × 100.

Examination was made in four cases of ependymoma in which roentgen rays were not administered. The specimens were obtained at successive operations, the interval varying from five to eighteen months. In one case a few mitoses appeared in the second specimen. A greater number of astrocytes occurred in one portion of the second specimen in another case. In the third case the last specimen showed a greater tendency toward clumping of nuclei. In a fourth case a considerable increase in mitotic figures occurred in the second specimen, obtained

nine months after the first. The more clearly defined multinucleated cells seen in the postirradiation specimens did not occur in the control cases.

OLIGODENDROGLIOMA

The changes observed in a single case after treatment with roentgen rays were essentially the same as those encountered in a control case. No areas showing differentiation of cells toward astrocytes, such as occurred in the postirradiation specimen, were encountered in the control case. However, the fact that such a differentiation occurred in an ependymoma used as a control renders it likely that a smilar change may occur in a nonirradiated oligodendroglioma. Examination of specimens in a second control case revealed essentially no histologic difference in the two specimens, taken eleven months apart.

COMMENT

After irradiation tumor cells may become considerably larger, and multinucleated cells frequently occur. All stages, from slight swelling of the nucleus to marked ballooning and vacuolation, may be encountered. In other cases, particularly in medulloblastoma, the degenerative changes assume the form of pyknosis and karyorrhexis, and shrinkage of cells may occur. The fact that after irradiation cells may become larger does not indicate an increase in maturity. Spongioblasts as well as astrocytes occurred among the large cells in postirradiation specimens of glioblastoma multiforme. The focal necrosis which sometimes follows irradiation seems at times to be the result of direct lethal action on the tumor cells rather than to be secondary to vascular change. Blood vessels in the region of necrosis often appear normal. Although endothelial swelling or proliferative vascular changes may occur, thrombosis is less common.

The preponderance of fibrous tissue in the spinal tumor implant in the case of the cerebral ependymoma raises the question whether it resulted from irradiation. It is recognized that in medulloblastoma subarachnoid tumor implants may contain more connective tissue than the original cerebellar tumor (Bailey[2]). In cases of ependymoma subarachnoid tumor implants are rare. However, in the one case of ependymoma of the temporal lobe reported by Cairns and Russell,[8] in which glistening nodules, the size of a pinhead, occurred in the midthoracic region of the spinal cord, collagen did not occur among the tumor cells. Nevertheless, that the occurrence of connective tissue in the spinal tumor resulted from roentgen irradiation does not seem

8. Cairns, H., and Russell, D. S.: Intracranial and Spinal Metastases in Gliomas of the Brain, Brain **54**:377, 1931.

likely, for two reasons: 1. The degenerative changes in the tumor were mild, and in the other gliomas it was observed that the increase in connective tissue paralleled the degeneration of the tumor. 2. One would have expected more striking evidence of fibroblastic proliferation in the other postirradiation specimens of the tumor if the increase in connective tissue had resulted from roentgen irradiation. Moreover, radiation was not applied directly to the cervical portion of the spinal cord. It seems more likely, then, that the great amount of fibrous stroma of the spinal nodule is attributable chiefly to its environment. The great increase in mitotic figures in the second specimen of a control case of ependymoma indicates the extent to which a tumor may change in the course of its lifetime. It is important, therefore, not to overestimate the possible rôle of irradiation in stimulating the tumor in C. S. (case 25), with its resultant subarachnoid spinal implant.

Extensive degenerative changes in tumor cells, with considerable proliferation of connective tissue, occurred in the postirradiation specimen from one of the astrocytomas (J. P.). Much of the brain near the tumor presented thickening of the blood vessels with, occasionally, hyalinization of their walls leading to occlusion. One sometimes observes in postoperative material thickening of blood vessels, probably as an inflammatory reaction resulting from the hemorrhage associated with operation. The extent of the various degenerative and proliferative changes in this case exceeded that which one sees after operation alone; this would seem to be attributable to roentgen irradiation. Degeneration of ganglion cells leading to complete neuronophagia occurred chiefly in the vicinity of the tumor. These changes were most intense in regions in which the vascular changes mentioned were most marked. The damage to the nerve cells might, therefore, be secondary to the changes in the blood vessels, although a primary effect of the roentgen rays on the nerve cells, as well as on the interstitial cells, is possible. Degenerative vascular changes were demonstrated by Lyman, Kupalov and Scholz [9] in brains of adult dogs after heavy doses of roentgen rays. These authors regarded the effect of roentgen rays to be primarily on blood vessels rather than on the cells of the cerebral cortex. The involvement of much of the entire brain and spinal cord by the tumor brings up the question of the rôle which the irradiation may have played in stimulating the growth of the tumor. The range of pattern encountered after irradiation was greater than that seen in the original specimens. Greater numbers of less differentiated cells occurred in the postirradiation tumor. It is known that there are

9. Lyman, R.; Kupalov, P., and Scholz, W.: Effect of Roentgen Rays on the Central Nervous System: Results of Large Doses on the Brains of Adult Dogs, Arch. Neurol. & Psychiat. **29**:56 (Jan.) 1933.

tumors which at reoperation present features of less differentiated glioma without any roentgen radiation having been administered in the interval. However, the prominence of subpial aggregates of cells in many areas, together with the widespread involvement of the brain by tumor and the presence of subarachnoid spinal tumor implants, is at least suggestive that roentgenotherapy may have exerted a stimulative effect on the tumor.

It is difficult to draw reliable conclusions from a small series of cases in which roentgen rays were administered in different doses over varying periods. In some of the cases studied it is possible that the absence or scarcity of histologic alterations may be related to the long interval after irradiation before the second specimen was obtained. It is likely that after a certain period during which the tumor may be held in restraint by roentgen rays, it approaches its original activity. The exact period during which a given amount of roentgen rays may exert this restraining influence and its extent cannot at present be determined. Nor can one, on the basis of these cases, answer the question whether intensive doses of roentgen rays delivered within a short period or divided doses delivered over a longer interval are more effective in checking the growth of the tumor. The fact that the extent of damage to the brain adjacent to the tumor in most of these cases was not serious indicates that greater doses of roentgen rays might often have been administered. On the other hand, it is important to recognize the harmful effects of large amounts of radiation on the brain, as in J. P. (case 23).

One cannot be certain that the differentiation of tumor cells toward adult neuroglia and ganglion cells in G. S. was caused by roentgen rays. It seems likely, however, in view of the observations in the other cases of medulloblastoma that irradiation did play a part in the extensive fibrosis. The occurrence of ganglion cells and neuroglia cells embedded within collagen stroma would seem to indicate a greater resistance of these cells than of tumor cells to roentgen rays. That the effect of roentgen rays may be distributed irregularly throughout a tumor is indicated in the cases of medulloblastoma. Whereas evidence of regression of the tumor occurred in large areas, other regions were cellular, presenting at times numbers of mitotic figures. Complete sterilization of the tumor was not accomplished in any of these cases. If this is possible in any glioma, the medulloblastoma would seem to be the most promising, since it is more sensitive to roentgen rays than the other gliomas. Such an ideal outcome would depend on the determination of a dose of roentgen rays lethal for all tumor cells but not seriously or permanently injurious to adjacent nerve tissue. Whether this is possible remains to be seen. In general, it appears that the larger doses of roentgen rays exert the more marked effects on the

tumor cells and on the biologic activity of the neoplasm. This has seemed particularly true in the cases of medulloblastoma; yet there are several exceptions to this statement in this series of cases, and strict correlation of the histologic changes and the period of survival with the dosage of roentgen rays cannot be applied. A number of variables must be considered in an attempt to correlate tumors roentgenologically, histologically and clinically, namely, the rate of administration as well as the dose of roentgen rays, the interval between the last roentgen treatment and the time at which the tumor tissue was obtained, the exact location of the tumor, the nature of the operative procedure and the size of the tumor (since the depth dose may vary to some extent in different portions of a large tumor). All these requirements are not fulfilled by the present series. Such an ideal group of cases would not be readily available. The present series serves merely to indicate that certain types of glioma are more sensitive than others to roentgen rays and that the possibility of a stimulative effect of roentgen rays, in some cases with damage to the brain, must be kept in mind.

SUMMARY

Histologic regression of a tumor following roentgenotherapy is associated with degenerative changes and an increase of connective tissue in the tumor. These changes were most marked in the cases of medulloblastoma. Postirradiation specimens in two of the eight cases of glioblastomas presented a slight increase in necrosis, with proliferation of connective tissue—changes, however, which may well occur within the range of variation in glioblastoma. More definite evidence of histologic regression following irradiation occurred in a third case (C. B.), in which there was extensive cyst formation and considerable connective tissue scarring. The changes in the tumor were more marked than those which I have observed in nonirradiated glioblastoma and are probably attributable to the roentgenotherapy. At least, it seems justified, on the basis of the suggestive evidence in this case, to continue treating glioblastoma with large doses of roentgen rays. The postirradiation specimens in both cases of astroblastoma presented increased degeneration, with proliferation of fibroblasts. The changes were mild, and more intensive irradiation might have resulted in more convincing evidence of histologic regression. A slight increase in connective tissue stroma followed irradiation in the single case of medullo-epithelioma. In one case of ependymoma increased degeneration, with cyst formation and proliferation of connective tissue, occurred in the postirradiation specimen. These changes were greater than those observed in the control cases. In the second case of ependymoma there was the unusual occurrence of a subarachnoid tumor implant removed from the cervical

portion of the spinal cord after considerable irradiation had been directed to the tumor in the left temporal region. A great increase in the number of mitoses was noticeable in the nodule in the spinal cord. The two specimens in the case of oligodendroglioma presented no greater difference than those observed in the control case. In not one of four cases was astrocytoma of the fibrous type markedly affected by irradiation. The tumor in the fifth case originally contained numerous astrocytes of the plump cell type, many of which were multinucleated. After irradiation an increase in the number of multinucleated cells and mitoses occurred. The last patient (J. P.) with astrocytoma presented striking changes after irradiation. Extensive degeneration in tumor cells and blood vessels occurred, with connective tissue scarring. At the same time there was growth of tumor throughout the brain, with spinal subarachnoid tumor implants. Polar spongioblasts predominated in many portions of the tumor. There was evidence of damage to the blood vessels and nerve cells of the brain.

CONCLUSIONS

Medulloblastoma was the only glioma in the series studied in which there was convincing evidence of a uniformly beneficial effect of roentgenotherapy.

The possibility that some tumors may become less differentiated and more rapidly growing after irradiation is suggested by (1) case 23 (J. P.), in which widespread growth of tumor throughout the brain and subarachnoid space occurred, and (2) the occurrence of a subarachnoid spinal implant of ependymoma presenting an increase in mitotic figures (C. S. [case 25]).

In administering large doses of roentgen rays, one must recognize the possibility of damage to blood vessels (with hemorrhage and softening) and to nerve cells of the brain, evidence of which occurred in J. P. (case 23).

Dr. A. N. Arneson of the department of Radiology of the Washington University School of Medicine calculated the threshold doses of roentgen rays given in the table.

Welfare Island, New York City.

POLIOMYELITIS (POLIOMYELOPATHIA) CHRONICA

REPORT OF A CASE, WITH HISTOLOGIC STUDY

ALBERT T. STEEGMANN, M.D.

CLEVELAND

In 1865 Prevost and Vulpian first described atrophy of the anterior horns and anterior horn cells in infantile paralysis and demonstrated the relation of these changes to the reduction in volume of the white substance and the localization of the disease at a definite level. This led Charcot and Joffroy to the conception of the relationship of amyotrophy to primary disease of the anterior horn cells. Subsequently, Charcot and others pointed out that patients who have survived an attack of acute anterior poliomyelitis may later show progressive spinal muscular atrophy. Spinal nuclear amyotrophies related to trauma, syphilis and diabetes, as well as to preexisting acute poliomyelitis, have been termed poliomyelitis chronica. Salmon and Riley [1] found references to fifty-six cases in the literature and reported three additional cases of poliomyelitis chronica in which there was a history of a previous attack of acute poliomyelitis. Only two of these cases were in women. Postmortem examinations have been reported by Landouzy and Dejerine,[2] Bernheim,[3] Cornil and Lepine,[4] Hayem,[5] Vulpian,[6] Hirsch,[7] Pastine [8] and Dimitri.[9] Only Dimitri's cases were

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From the Departments of Pathology and Medicine, the City Hospital and the Western Reserve University School of Medicine.

1. Salmon, Leon A., and Riley, Henry Alsop: The Relation Between Chronic Anterior Poliomyelitis or Progressive Spinal Muscular Atrophy and an Antecedent Attack of Acute Anterior Poliomyelitis, Bull. Neurol. Inst. New York **4**:35, 1935.

2. Landouzy, L., and Dejerine, V.: Des paralysies générales spinales à marche rapide et curable, Rev. de méd. **2**:645, 1882.

3. Bernheim: Des poliomyélites antérieures, aigüe, subaigüe et chronique de l'adulte greffées sur la paralysie infantile, Rev. de méd. **13**:1, 1893.

4. Cornil and Lepine: Sur un cas de paralysie générale spinale antérieure subaigüe, suivi d'autopsie, Compt. rend. Soc. de biol. **2**:75, 1876.

5. Hayem, G.: Une altération musculaire consécutive à une paralysie infantile, Compt. rend. Soc. de biol. **1**:256, 1870.

6. Vulpian, A.: Paralysie atrophique de l'enfance, ayant dans son évolution procédé par poussées successives. Surcharge adipeuse dans les régiones envahies par l'atrophies, Clin. méd. de l'hôp. de la Charité, 1879, p. 778.

7. Hirsch, William: On the Relations of Infantile Spinal Paralysis to Spinal Disease of Later Life, J. Nerv. & Ment. Dis. **26**:269, 1899.

(Footnotes continued on next page)

studied by modern methods. Excellent studies by Medea [10] and Cassirer and Maas [11] of cases in which there was no antecedent history of acute poliomyelitis have contributed to the pathology of the condition. Marburg,[12] Dimitri [9] and Salmon and Riley [1] described clinical details which will not be repeated in this report, except to an extent sufficient to clarify certain clinical features.

REPORT OF CASE

Clinical History.—R. S., a white woman aged 20, was admitted to the City Hospital (service of Dr. J. A. Toomey) on Nov. 29, 1933, and remained until Nov. 25, 1934. She was readmitted on Dec. 15, 1934, and remained until her death, on Jan. 5, 1935. Six weeks before the first admission she had had a "head cold," blurring of vision and difficulty in urination. Two weeks later gastrointestinal symptoms appeared—nausea, vomiting, epigastric pain and constipation—for which she was admitted to the hospital.

The patient had had acute anterior poliomyelitis with paralysis of the legs at the age of 2½ years. Between the ages of 8 and 12 she had submitted to four operations for the stabilization of joints, after which she could walk well. Otherwise, her health had been good.

Physical Examination.—Examination by systems gave normal results except in the central nervous system. No defects of the cranial nerves were present. The tendon reflexes were absent in the lower extremities and somewhat diminished in the left arm. Atrophy and weakness of the muscles of the legs and weakness of the muscles of the thighs were present. No atrophy or paresis was found in the arms. The abdominal reflexes were absent. No Babinski sign was present. There was ankylosis of the ankle joints.

Laboratory Examination.—The urine was normal, and the spinal fluid was clear and under a pressure of 11 mm. of mercury. It contained 7 mononuclear and 4 polymorphonuclear cells per cubic millimeter. The Pandy test gave a two plus reaction. The Wassermann reaction of both the blood and the spinal fluid was negative.

Course.—During the first month of hospitalization there developed profound muscular weakness associated with pain in the muscles. Shortly after her admission, the patient began to show a septic temperature, which ranged to 38.8 C. (101.8 F.) and lasted about a month. At about this time pus and albumin appeared

8. Pastine, C.: Deux cas d'amyotrophie chronique consécutive à la paralysie spinale dont l'un avec examen anatomique, Rev. neurol. **19**:466, 1910.

9. Dimitri, V.: Amiotrofías tardias progresivas en casos de parálisis infantil. (Estudio anátomo-clínico), Semana méd. **2**:1002 (Oct. 13) 1932; Las lesiones bulbares en la poliomielitis crónica: Estudio anátamo-clínico de tres observaciones personales, Prensa méd. argent. **19**:33 (June 10) 1932; Amiotrofías tardias progresivas en casos de parálisis infantil, Rev. Asoc. méd. argent. **46**:1079, 1932.

10. Medea, E.: Beitrag zur Kenntnis der Poliomyelitis anterior subacuta adultorum, Monatschr. f. Psychiat. u. Neurol. **23**:17, 146, 255 and 341, 1908.

11. Cassirer, R., and Maas, Otto: Über einen Fall von Poliomyelitis anterior chronica, Monatschr. f. Psychiat. u. Neurol. **24**:306, 1908.

12. Marburg, Otto: Die chronischen progressiven nucleären Amyotrophien, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 278.

in the urine, and the condition persisted despite treatment until death. The degree of muscular weakness varied from time to time but improved near the end of the first hospitalization. No definite objective sensory changes were found, but the patient continued to complain of pain in the muscles. Diplopia, strabismus and other defects of the cranial nerves were never observed. The spinal fluid was reexmained on Dec. 12, 1933, with the following results: fluid, clear; pressure, 12 mm. of mercury; cells, 12 mononuclears per cubic millimeter; Pandy test, four plus and gum mastic curve, 2110000000. On Dec. 15, 1933, weakness was noted in the arms, for the first time. A few days later all extremities were weak. At the time of discharge the muscles were stronger and the patient could walk with support, but interosseous atrophy had begun in the hands.

Second Admission.—Three weeks after her discharge from the hospital, the patient was readmitted because of return of the gastro-intestinal symptoms and difficulty in breathing. She complained of pain and heaviness in the legs. Fluids given by mouth were promptly vomited. The patient had been unable to void for twenty-six hours. On neurologic examination, no defects of the cranial nerves were found. Examination of the muscles revealed atrophy of the interosseous muscles of the hands. The dorsiflexor muscles of the hands, the extensor muscles of the fingers and the abductor muscles of the thumbs were all weak. Likewise, the muscles of the abdomen and thighs were weak and atrophic, especially the extensor muscles of the right thigh. The muscles of the legs were markedly atrophic, as had been observed previously. The tendon reflexes of the lower extremities and the abdominal reflexes were all absent. The tendon reflexes of the arms were sluggish. No sensory defects or signs of involvement of the pyramidal tract were elicited. All extremities became progressively weaker until the patient was unable to move them voluntarily. She continued to complain of pain in the muscles. Signs of bronchopneumonia appeared twenty-six hours before her death, which occurred three weeks after the second admission and approximately fifteen months after onset of the illness. Cessation of respiration occurred before the heart stopped beating. Laboratory studies during the second period revealed nothing remarkable in the spinal fluid or gastric juice. The urine still contained pus and albumin. Roentgen examination of the gastro-intestinal tract gave normal results except for marked dilatation of the proximal two thirds of the duodenum.

Gross Pathologic Examination.—Autopsy was performed by Dr. H. H. Heitzman, five and a half hours after death. The anatomic diagnosis from routine study of the organs, exclusive of the central nervous system, was: bronchopneumonia; edema of the lungs; chronic cholecystitis; subacute cystitis; chronic rheumatic heart disease with mitral valvulitis; calcified tuberculous complex of the lower lobe and bifurcation node of the left lung; moderate dilatation of the duodenum and small adenomas of the adrenal cortex.

Brain and Spinal Cord: Grossly the brain appeared moderately swollen (weight, 1,445 Gm.) and hyperemic but otherwise exhibited no abnormalities. The leptomeninges of both the brain and the spinal cord were thickened and cloudy. Reduction in size of the anterior horns of the spinal cord could be seen grossly at all levels.

Histologic Examination.—Frozen and pyroxylin sections of the nervous system were stained by the Nissl, Hortega (Kanzler), Cajal (Corten), Holzer, Bielschowsky, Van Gieson, Achucarro (tannin-silver), Marchi, Unna-Pappenheim and myelin sheath (Weil and Spielmeyer) methods and scarlet red and hematoxylin and eosin.

Spinal Cord: In all sections of the spinal cord the leptomeninges were thickened and stained dense red with the Van Gieson stain (fig. 1), indicating a large amount of collagenous connective tissue. Only occasional lymphocytes and chromatophoric cells were seen in the meshes, and there were no perivascular round cell infiltrations. The collagenous connective tissue was abundant in the adventitia around the radicular blood vessels, extending from the subarachnoid space into the substance of the funiculi, as well as in the nerve roots, especially the anterior roots. With the Achucarro tannin-silver stain, argentophilic mesenchymal fibers could be seen lying beneath the pia, beside the spinal cord.

The anterior horns were atrophic and shrunken perhaps a third of their normal diameter, and showed marked loss of cells. In some of the sections of the lumbar region, which was most severely diseased, only one or two cells remained in the anterior horns, and the architectural arrangement of the cell groups was difficult to

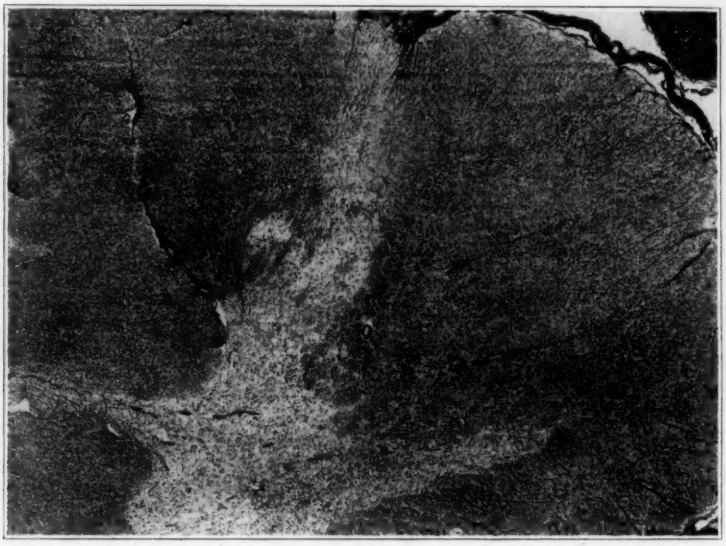

Fig. 1.—Section of the cervical segment showing increased connective tissue in the leptomeninges and around the blood vessels in both the gray and the white matter. Van Gieson stain; × 20.

identify or was lost in all regions except the upper cervical and sacral segments. The number and arrangement of the anterior horn cells were best preserved at the sacral levels, where the qualitative changes in the cells demonstrated that they were in the process of degeneration. The lateral horn of the gray matter was degenerated in the lumbar region and partially so in the dorsal region. In one section of the lower cervical region the ventrolateral cell group on one side and the dorsolateral on the other were the only groups left. The qualitative changes in the nerve cells of the anterior horn were best demonstrated in the sacral region (fig. 2). In addition to normal ganglion cells, central chromatolysis with displacement of the nucleus (axonal reaction), shrunken cells with concave borders, deep-stained cytoplasm and snakelike processes and cell shadows could be seen. There were also clumps of nuclei of oligodendroglia cells shaped like ganglion cells, which might be interpreted as the replacement of ganglion cells by neuroglia cells Glia cell satellites around the ganglion cells were frequently observed. In the other

regions of the spinal cord shrinkage was the most frequent type of change in the ganglion cells and this was not associated with an increase of lipoid pigment. Cell shadows were occasionally seen.

The aforementioned changes in the ganglion cells were associated with a marked increase of the fixed glial elements in both the gray and the white matter (fig. 3). Glial nodes were also seen frequently. Most of the glia cells consisted of astrocytes, with scanty cytoplasm and early regressive changes in the nuclei. The Hortega stain showed few microglia cells. Most of the cells were oligodendroglia cells, many of which were swollen in the sense of Penfield and Cone. These cells were abundant in both the gray and the white matter. With the Holzer stain an intense, irregular fiber gliosis, without the presence of giant astrocytes, was seen in the anterior horns and around the central canal (fig. 4). This extended into the white matter, where it became more isomorphic. The gliosis was most intense in the lumbar region but was strong at all other levels of the cord. The

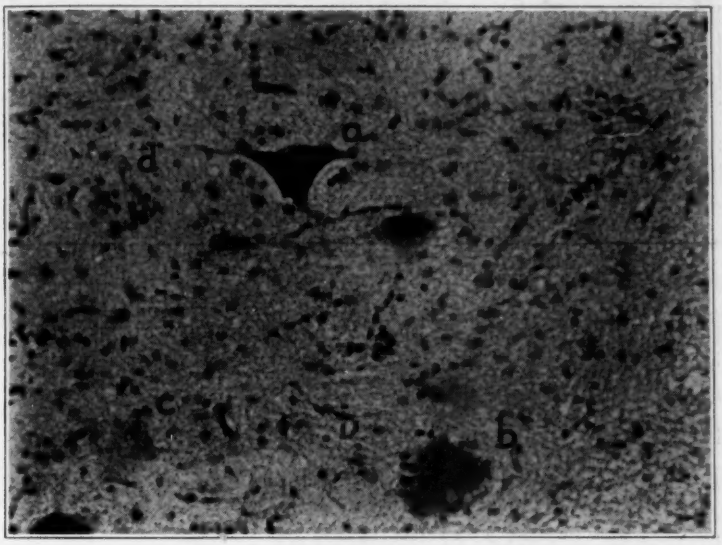

Fig. 2.—Anterior horn of the sacral region. *a* indicates a shrunken anterior horn cell; *b*, a cell with central chromatolysis, displaced nucleus and round contour typical of the axonal reaction; *c*, a cell in which the shadow is hardly visible but the nucleus is still visible near the upper pole, and *d*, a clump of glia nuclei which have probably replaced a degenerated ganglion cell. Nissl stain; × 217.

anterior horn cells were lying in an intense glial scar. There was also abundant collagenous connective tissue around the small arteries and arterioles of the anterior horns. A row of glial satellites was frequent along the small vessels, but no infiltration of round or plasma cells was seen. The same degree of vascular changes was not observed in the posterior horns. The ependymal cells around the central canal were proliferated, but there was no degeneration of the syringomyelic type. Rossolimo [13] stated that syringomyelia occurs in 33 per cent of cases of chronic poliomyelitis.

13. Rossolimo, G.: Ueber Poliomyelitis anterior chronica und Syringomyelia, Neurol. Centralbl. **22**:388, 1903.

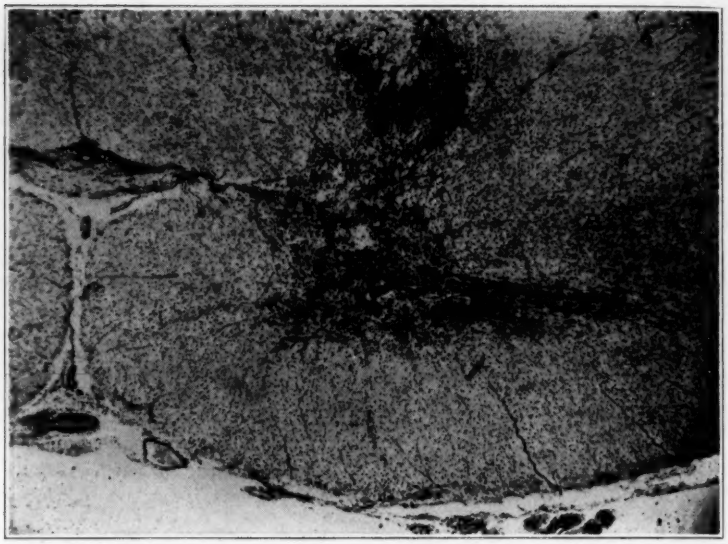

Fig. 3.—Cervical segment of the cord, showing increase of fixed glia elements, loss of anterior horn cells and shrinkage of the anterior horn. Nissl stain; × 20.

Fig. 4.—The cervical region of the spinal cord, showing intense fiber gliosis and shrinkage of the anterior horn. The glia fibers extend into the white matter and along the anterior roots and blood vessels. Holzer stain; × 20.

In the white matter of the spinal cord isomorphous gliosis was present, especially around the periphery and near the gray matter, being less intense in the zone between. Fiber gliosis along the nerve roots, especially the anterior, was also prominent. The radicular vessels showed not only the perivascular collagenous connective tissue already described but marked perivascular fiber gliosis, accompanied by astrocytes and swollen oligodendroglia cells. This produced prominent

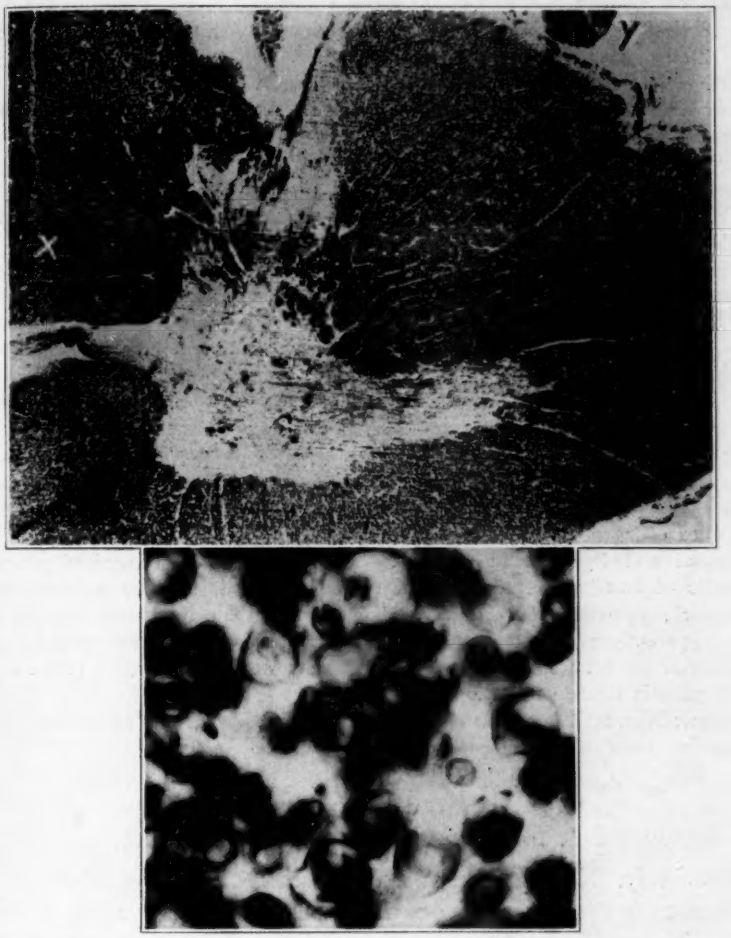

Fig. 5.—The upper view of the cervical portion of the cord shows the diffuse light appearance of the myelin fibers, the loss of myelinated fibers in the gray matter of the anterior horn and the contrast between the white matter and the posterior root, indicated at *Y*. Weil stain; × 20. The lower view, taken from the region marked *X* in the upper part of the figure, shows the swelling and poor staining quality of the myelinated fibers of the white matter of the spinal cord. Oil immersion; × 1,500.

septal markings (fig. 4). Argentophilic connective tissue was not nearly as abundant as the collagenous variety around the blood vessels. In myelin sheath

preparations the white matter of the spinal cord showed a diffuse light appearance in all regions (fig. 5). The fibers showed definite swelling, which appeared as ballooned areas in longitudinal sections. This apparently accounted for the light appearance, as no appreciable degree of falling out of myelinated fibers could be seen. This process was not accompanied by products of fatty degeneration with either the Marchi or the fat stain. A few droplets of fat could be seen in an occasional fixed glia cell. The clearing of myelin sheaths was most evident in the posterior and lateral columns of the sacral region and in all funiculi of the dorsal and cervical regions, where the posterior columns were spared to a greater degree than in the other regions of the white matter. The anterior nerve roots were strongly demyelinated, with a secondary overgrowth of mesoblastic connective tissue, while the posterior roots contained some mesoblastic connective tissue but were not demyelinated.

Brain: The changes in the rest of the central nervous system were much less intense than those in the spinal cord, and probably represented either residual changes from the former acute infection or mild degenerative changes associated with the same process described in the cord. They consisted for the most part of diffuse proliferation of the fixed glial elements in both the gray and the white matter in all regions. This was quite marked in the region of the dentate nucleus of the cerebellum, where there were some dropping out and shrinkage of ganglion cells—probably a residual trace of the preexisting acute poliomyelitis. Some cells of the dorsal vagal nuclei exhibited shrinkage. The subependymal and mild subcortical isomorphous gliosis seen in many degenerative processes was present. The ganglion cells of the cortex and basal ganglia were normal. The leptomeninges of the cortex were less thickened than those of the cord but contained red cells and mononuclear cells of reticulo-endothelial type. The meningeal veins were greatly dilated and packed with red cells. Only the larger blood vessels of the cortex contained collagenous connective tissue.

Spinal and Sympathetic Ganglia: The ganglion cells contained abundant granules of black pigment, and some of the cells had shrunken pyknotic nuclei with dark, vacuolated or disintegrated cytoplasm. The interstitial capsule cells were apparently proliferated in many areas, and this was accompanied by some increase of the connective tissue. These changes were more evident in the dorsal spinal ganglia than in the sympathetic ganglia.

Sciatic Nerve: There was marked loss of nerve fibers, with an increase of the connective tissue of the epineurium and perineurium.

COMMENT

The disease in this case was degenerative, proliferative and noninflammatory. No plasma cells were present. The degree of round cell infiltration in the leptomeninges and around the blood vessels observed occurs in many degenerative diseases of the central nervous system. The term "poliomyelitis" is a misnomer. Although shrinkage of anterior horn cells occurs in progressive spinal muscular atrophy, amyotrophic lateral sclerosis and other related processes (Spielmeyer[14] and Medea[10]), the absence of excessive lipoid pigment in these cells is unusual and may be

14. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 282.

due to the youth of the patient and the chronicity of the process. That central chromatolysis (axonal reaction) often represents some type of pathologic process other than a retrograde change secondary to primary injury to the axis-cylinder (Spielmeyer [15] and Peter [16]) is proved here, for no acute or early degenerative changes were present in the anterior roots or the peripheral nerves. The degeneration of the anterior horn cells is the result of a primary disease process dependent on factors other than degeneration of the peripheral nerves. The degree of gliosis in the anterior horn is more pronounced than that in most progressive spinal muscular atrophies and must be in part residual changes from the former acute infection. The glial fibrosis which spread from the anterior horns into the funiculi is what Hirsch [7] described in his case as "connective tissue." Hirsch's case and the one described in this paper illustrate bridging of the gap betewen the conditions which Schröder [17] called the "polioclastic" and "myelinoclastic" processes in the spinal cord. Penfield and Cone [18] observed swollen oligodendroglia cells in acute poliomyelitis, although Warburg [19] did not see this change in later stages of the disease in monkeys. The cells may be related to injurious metabolic factors induced by terminal illness or by the degenerative disease itself.

In most cases of poliomyelitis chronica there is involvement of the white matter of the spinal cord (Cassirer and Maas [11]). The diffuse light appearance of the spinal cord with stains for myelin sheaths in this case, which was not associated with products of degeneration in Marchi and fat stains, is observed in old, inactive or healed processes. This may not be the correct interpretation in slowly progressive degenerative diseases. Swollen, myelinated fibers with poor staining quality, rather than loss of fibers, were observed in the pre-Marchi stage of myelitis by Henneberg.[20] Perhaps the picture can be produced by colloidal

15. Spielmeyer,[14] p. 267.

16. Peter, Cuno: Beitrag zur Klinik und pathologischen Anatomie der hereditären Nervenkrankheiten, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:543, 1927.

17. Schröder, P.: Myelitis und Poliomyelitis, Deutsche med. Wchnschr. **51**: 973 (June 12) 1925.

18. Penfield, Wilder, and Cone, William: Acute Swelling of Oligodendroglia: A Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926.

19. Warburg, Bettina: Experimental Poliomyelitis: Histology of the Persistent Lesions of the Central Nervous System, Arch. Neurol. & Psychiat. **25**:1191 (June) 1931.

20. Henneberg, Richard: Die Myelitis und die myelitischen Strangerkrankungen, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 694.

chemical changes in the nerve fiber—changes which, according to von Braunmühl,[21] play an important part in degenerative diseases.

The arguments and discussions in the earlier medical literature [22] concerning the relationship existing between chronic poliomyelitis and polyneuritis, between poliomyeltis chronica and degeneration of the anterior horns associated with various types of degeneration of the fiber tracts or between the chronic form of poliomyelitis and progressive spinal muscular atrophy throw little light on the pathogenesis of this disease. Likewise, attempts at rigid nosologic differentiation of these many related processes break down so long as the pathogenetic elements are poorly understood. That an acute attack of poliomyelitis may predispose a person to the development of progressive spinal muscular atrophy, with or without associated degeneration of fiber tracts, has been maintained by Marburg,[12] Oppenheim [23] and Potts.[24]

Many theories of pathogenesis have arisen in the past half-century.[25] Bernheim, Sterne, Laehr, Strümpell and Charcot favored the theory of a diathesis or tendency to inflammation in the anterior horn, which could be either congenital or acquired through the intermediation of a germ. Probst, Oppenheim, Rose and Brissaud claimed that congenital weakness of the anterior horn cells is the greatest factor. Gowers, Charcot and Oppenheim contended that a new infection may attack the old scar first as a locus minoris resistentiae. Chiappori [26] expressed the belief that a preceding acute attack of poliomyelitis injures the anterior horn cells so as to affect their viability and lead thus to early degeneration and death. This conception could be used to explain the accessory biologic factors, such as exposure, fatigue, trauma and infection, discussed by Potts and Dimitri. Hirsch [7] based his explanation of the disease on his histologic observations. He said that the disease is a diffuse interstitial myelitis, of vascular origin, with secondary degeneration of nerve cells. Kroll [27] stated that the degeneration is due

21. von Braunmühl, A.: Versuche um eine kolloidchemische Pathologie des Zentralnervensystems: Das synaeretische Syndrom als cerebrale Reaktionsform, Klin. Wchnschr. **13**:897 (June 23); 937 (June 30) 1934.

22. Reviewed by Medea [10] and Cassirer and Maas.[11]

23. Oppenheim, H.: Textbook of Nervous Diseases for Physicians and Students, Edinburgh, O. Schulze & Co., 1911, vol. 1, p. 214.

24. Potts, Charles S.: A Case of Progressive Muscular Atrophy Occurring in a Man Who Had Had Acute Poliomyelitis Nineteen Years Previously, with a Review of the Literature Bearing upon the Relations of Infantile Spinal Paralysis to the Spinal Diseases of Later Life, Univ. Pennsylvania M. Bull. **16**:31 (March) 1903.

25. Salmon and Riley.[1] Dimitri.[9] Oppenheim.[23]

26. Chiappori, Romulo: Poliomyelitis crónica; Recidiva tardía de la amiotrofía en una parálisis infantil, Rev. Asoc. méd. argent. **35**:257 (May-June) 1922.

27. Kroll, M.: Die neuropathologischen Syndrome, zugleich Differentialdiagnostik der Nervenkrankheiten, Berlin, Julius Springer, 1929, p. 17.

to the increasing demands made on a weakened structure and agreed with Zakarchenko [28] that there is a possibility that the late disease may be due to recurrent acute poliomyelitis. Except for the theory of abiotrophy, the aforementioned conceptions are vague and of little value.

Could this disease result from recurrent acute poliomyelitis? Cases of recurrent acute poliomyelitis have been reported by Tesdal,[29] Loeschke,[30] Moore,[31] Still [32] and Quigley.[33] That in some of these cases there was really recurrent poliomyelitis is open to reasonable doubt, considering the incompleteness of histologic and immunologic studies made in such cases up to the present. Spielmeyer [34] maintained that in acute poliomyelitis the virus exerts its influence for only a short time, in the earliest stage of the disease, and that later vascular and other reactive phenomena seen in the tissues are a secondary reaction to tissue damage. This conception agrees with the clinical course of the disease.

In the case described here, the clinical course was progressive, and the histologic features were atypical for poliomyelitis and other types of virus infection. The cases described by Poursines [35] as instances of "subacute poliomyelitis" due to a "neurotropic" virus resembled this case clinically, but no proof of the "neurotropic" virus was offered. Wickman [36] stated that progressive spinal muscular atrophy, or poliomyelitis chronica, may be the result of an abortive attack of acute anterior poliomyelitis which was not recognized. This theory will not explain the familial forms of progressive spinal muscular atrophy.

A theory to explain this disease must take into consideration the histologic picture which fits into the conception of a "primary degenera-

28. Zakarchenko, M. A.: Kurss Nervnik Boleznay, Leningrad, 1930, p. 521; quoted by Salmon and Riley.[1]

29. Tesdal, Martin: A Second Attack of Poliomyelitis in the Same Patient After an Interval of Twenty-Four Years, Norsk mag. f. lægevidensk. **95**:978, 1934.

30. Loeschke, Adalbert: Ueber Rezidive bei Poliomyelitis, Kinderärztl. Praxis **5**:441, 1934.

31. Moore, Thomas: A Second Attack of Acute Poliomyelitis, Brit. M. J. **2**:166 (July 28) 1934.

32. Still, G. F.: Second Attacks of Acute Poliomyelitis, and the Minimal Duration of Immunity, Arch. Dis. Childhood **5**:295, 1930.

33. Quigley, T. B.: Second Attacks of Poliomyelitis: Review of Literature and Report of a Case, J. A. M. A. **102**:752 (March 10) 1934.

34. Spielmeyer, W.: Zur Histopathologie und Pathogenese der Poliomyelitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:159, 1932.

35. Poursines, Yves: Les poliomyélites subaiguës: Modalités cliniques et expressions lésionnelles, Encéphale **29**:31, 1934.

36. Wickman, Ivar: Beiträge zur Kenntnis der Heine-Medin'schen Krankheit, Berlin, S. Karger, 1907.

tive process." Spielmeyer [37] defined a primary degenerative process as a distintegrative process of the parenchyma, not dependent on inflammatory, circulatory or metabolic factors that can be recognized by present methods. In this case the picture differs from that of ordinary progressive spinal muscular atrophy in the more pronounced degree of proliferative reaction of the fiber-building glia and the connective tissue. Diffuse myelopathy may be seen in both conditions. The present case differs also in that there was a known etiologic factor which damaged the anterior horn cells and initiated the secondary tissue reactions contributing to the later disease process. Hirsch expressed the belief that the degeneration of nerve cells in his case was of vascular origin. A metabolic factor, which Edinger [38] considered in his theory to explain certain nervous diseases, appears to me of more significance. The proper combination of vascular or glial changes which resulted from the original acute disease possibly could interfere with the metabolism of the anterior horn cells.

Stimulation of cells, diseased or normal, leads to the production of metabolic waste products. It is conceivable that failure to eliminate these products could lead to deterioration. This might depend on the lymphatic drainage of the spinal cord, which influences the exchange of tissue fluids. Further studies on these processes (Orr [39]) and the way in which secondary changes in the tissues affect them will aid in the understanding of degenerative diseases of the cord.

Several clinical features are of interest: Since the patient had both chronic cholecystitis and urinary infection, which could explain the gastro-intestinal symptoms, the changes in the sympathetic ganglia are probably not significant. Furthermore, sympathetic ganglia removed from persons who had died of other causes showed changes similar to those described in this patient.

Pain in the muscles, without definite sensory changes, has been described in chronic poliomyelitis by Vulpian,[6] Hirsch,[7] Neuninger [40] and Medea.[10] Some contended that the pain is due to involvement of the posterior roots, while others attributed the pain to changes in the region of the central canal or in Gower's tract. Since pain is a frequent symptom in both syringomyelia and spinal muscular atrophy, irritation of the spinothalamic fibers in the region of the central canal offers a logical explanation.

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37. Spielmeyer, W.: Zum Problem der Systemerkrankungen, Jahrb. f. Psychiat. u. Neurol. **51**:256, 1934.

38. Edinger, L.: Eine neue Theorie über die Ursachen einiger Nervenkrankheiten, Samml. klin. Vortr. no. 106, 1894 (Inn. Med. no. 32, p. 87).

39. Orr, David: A Contribution to Our Knowledge of the Course of the Lymph Stream in the Spinal Roots and Cord. Rev. Neurol. & Psychiat. **1**:639. 1903.

40. Neuninger, cited by Potts.[24]

The patient in this case showed many of the clinical symptoms of this disease described by Marburg,[12] namely, occurrence of muscular paresis before atrophy, absence of fibrillary twitching, extension of the disease from the legs to the arms, absence of sensory changes, mild sphincteric disturbances and death from respiratory failure. A rigid clinical differentiation between poliomyelitis chronica and progressive spinal muscular atrophy cannot be made.

SUMMARY AND CONCLUSIONS

A case of poliomyelitis chronica in a patient who had had a previous attack of acute poliomyelitis is reported. Histologic study leads to the following conclusions:

1. Poliomyelitis chronica is a form of progressive spinal muscular atrophy.

2. A previous attack of acute poliomyelitis may predispose to the development of this disease.

3. The term poliomyelitis chronica is a misnomer, for the disease is a chronic, progressive, noninflammatory degenerative process.

In the case reported, the spinal cord showed shrinkage of the anterior horns at all levels, with chronic degenerative changes and loss of cells. This process was associated with pronounced gliosis of the anterior horns, extending into the white matter, increased fibrosis and gliosis around the blood vessels, fibrosis and thickening of the leptomeninges and diffuse myelopathy due to swelling of the myelinated fibers of the spinal cord. These changes were not accompanied by mobile or fixed products of degeneration.

Theories of the pathogenesis of chronic poliomyelitis are reviewed. The disease is considered to be a primary degenerative process of the anterior horn cells. Theoretically, this is considered to be due to metabolic factors, which can depend in part on the effect of the secondary tissue reactions in interfering with normal cell metabolism.

CONNECTIONS BETWEEN THE STRIATUM AND THE SUBSTANTIA NIGRA IN A HUMAN BRAIN

R. WAYNE RUNDLES, B.A.
AND
JAMES W. PAPEZ, M.D.
ITHACA, N. Y.

Maynard Shipley, an American writer and lecturer, died in San Rafael, Calif., on June 18, 1934, at the age of 62. The brain was removed by Mr. J. Ray Keaton, coroner of Marion County, Calif., and preserved in formaldehyde. Later it was sent to Ithaca, N. Y. The medical history was furnished by Dr. A. H. Mays, of Sausalito, Calif., who attended Mr. Shipley during his illness.

In his youth Shipley was an expert gymnast and athlete. His first serious illness occurred in 1922, when he was disabled for several months consequent to an attack of angina pectoris. Previously spells of faintness had been observed. In 1923 and 1924 he suffered paralysis of the right facial nerve, of a month's duration, following a dental extraction. In June 1931 and in August of the same year severe attacks of coronary occlusion occurred, from which he gradually recovered. The cardiac trouble recurred in October 1933 and persisted. On Feb. 16, 1934, he suffered cerebral occlusion, which resulted in right hemiplegia above the waist and motor aphasia. Although the blood pressure was below normal, general disseminated arteriosclerosis was present. Some recovery from this attack took place, since by the following June speech had returned sufficiently to be intelligible and he could sign his name fairly well. Mentally he was as keen as ever, although he was depressed emotionally. He could read as well as before; his reasoning powers were good, and his interests were unchanged. He was able to play the piano, although not with his former ability. On June 13 there began a series of attacks, cerebral and cardiac, which resulted in death on June 18.

Macroscopic examination of the brain confirmed the previous diagnosis of disseminated arteriosclerosis. The arteries were thin walled, and in some places the characteristic rings and patches produced narrowing of the arterial lumen amounting to virtual occlusion, although no actual thrombi were observed. The basilar artery and the anterior and middle cerebral arteries of the left side in particular were severely affected. After removal of the arachnoid and the pia mater, extensive cortical reduction and a few areas of softening were apparent (fig. 1). On the left side cortical atrophy was noted in the anterior temporal region, the superior and inferior parietal gyri, the insular cortex and the entire frontal lobe. The major cortical lesion, a yellow softening, involved the precentral gyrus below the caudal end of the superior frontal sulcus. The exposed cortex of the anterior subcentral gyrus was included in the softened area, as well as the cortex forming the anterior wall of the lower third of the central fissure. In its inferior tip the lesion extended slightly behind the fissure into the post-

From the Department of Anatomy, Cornell University Medical College.

central gyrus. All layers of the cortex were completely degenerated. Little of the underlying medullary material was affected. A slight superficial softening occurred also in the posterior end of the middle frontal gyrus. On the right side some atrophy of the cortex of the frontal lobe was noted, although it was less severe than that on the left. On this side there were small areas of superficial softening on the medial side of the paracentral lobule and in the posterior end of the middle frontal gyrus.

By circular incisions around the insulae the coronae radiatae were cut and the cerebral hemispheres removed, with the corpus callosum. The corpus callosum was reduced in thickness, and the head of the left caudate nucleus was atrophic and somewhat yellow. The cerebellar cortex was trimmed down to the basal nuclei, and the entire brain stem was prepared for microscopic study by the method of Pal and Weigert as modified by Ariëns Kappers. It was divided into two blocks at the level of the inferior colliculus, embedded in pyroxylin and cut transversely, at a thickness of 35 microns. The entire series of 2,150 sections was stained. We were unable to effect a satisfactory cell stain.

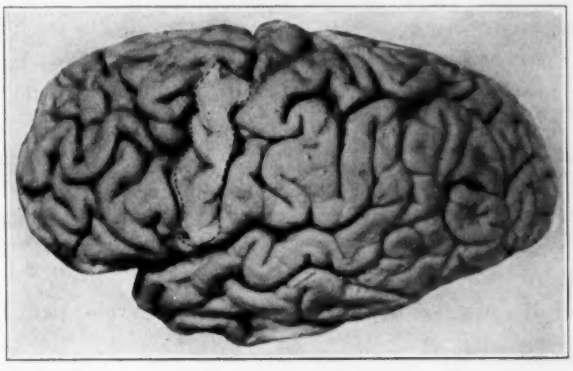

Fig. 1.—Photograph of the left cerebral hemisphere, showing cortical reduction and softening in the lower part of the precentral gyrus.

CORPUS STRIATUM

The striate bodies, or basal nuclei of the forebrain, have been frequently investigated and described as centers concerned with the coordination of muscular movement, muscle tonus and reciprocation and as regions of great clinical importance in chorea, athetosis, Parkinson's disease, carbon monoxide poisoning, epidemic encephalitis, etc. The clinical and anatomic researches of Dejerine,[1] Wilson,[2] the Vogts,[3]

1. Dejerine, J.: Anatomie des centres nerveux, Paris, J. Rueff, 1901.

2. Wilson, S. A. Kinnier: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427-492, 1914.

3. Vogt, C., and Vogt, O.: Zur Kenntnis der pathologischen Veränderungen des Striatum und des Pallidum und zur Pathophysiologie der dabei auftretenden Krankheitserscheinungen, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (Abt. B) **14**:1-56, 1919.

Hunt,[4] Jakob,[5] Foix and Nicolesco[6] and others provide the present conception of the anatomy, function, pathology and clinical symptomatology of the corpus striatum and associated centers in the dorsal thalamus, subthalamus and tegmentum. Recent authors have divided the corpus striatum on structural and functional grounds into two parts: the striatum, including the putamen and the caudate nucleus, and the pallidum, or globus pallidus.

It is the general opinion that the striatum receives impulses from the thalamus, being connected thus with the lower levels of the brain stem and with the cerebral cortex, and that it operates as a receptive and diffusion center for these impulses. The striatum, including the caudate nucleus and the putamen, is usually described as receiving such thalamic impulses and as projecting solely on the pallidum, which acts as the efferent nucleus for the entire corpus striatum and hence partially also for the thalamus and the systems beyond.

The division of the corpus striatum into the striatum and the pallidum is conveniently applied to clinical cases, because a striatal syndrome and a pallidal syndrome can be distinguished (Vogt and Vogt[3] and Jakob[5]). All cases are not, however, referable to two pure types, for in individual instances striatal and pallidal symptoms may be blended or additional related symptoms may be due to concomitant involvement of the dorsal thalamus, the subthalamic nucleus, the red nucleus, the substantia nigra or other components of the extrapyramidal system.

Although the involvement of the substantia nigra in paralysis agitans has been fairly well established, its significance and the part it may play in functional organization are still obscure. The anatomic evidence to be discussed here indicates that in addition to its prominent connection with the frontal cortex, the substantia nigra is closely related to the striatum (caudate nucleus and putamen) and that the important connections of the globus pallidus are with other nuclei of the subthalamus and the tegmentum.

The fiber connections of the corpus striatum have been described many times on the basis of Weigert preparations, both normal and pathologic, as well as in experimental studies utilizing the Marchi technic. The most evident structures are the radiating fasciculi of the

4. Hunt, J. R.: Progressive Atrophy of the Globus Pallidus, Brain **40**:58-148, 1917.

5. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923; The Anatomy, Clinical Syndromes and Physiology of the Extrapyramidal System, Arch. Neurol. & Psychiat. **13**:596-620 (May) 1925.

6. Foix, C., and Nicolesco, J.: Anatomie cérébrale: Les noyaux gris centraux et la région mésencéphalo-sous-optique suivi d'un appendice sur la maladie de Parkinson, Paris, Masson & Cie, 1925.

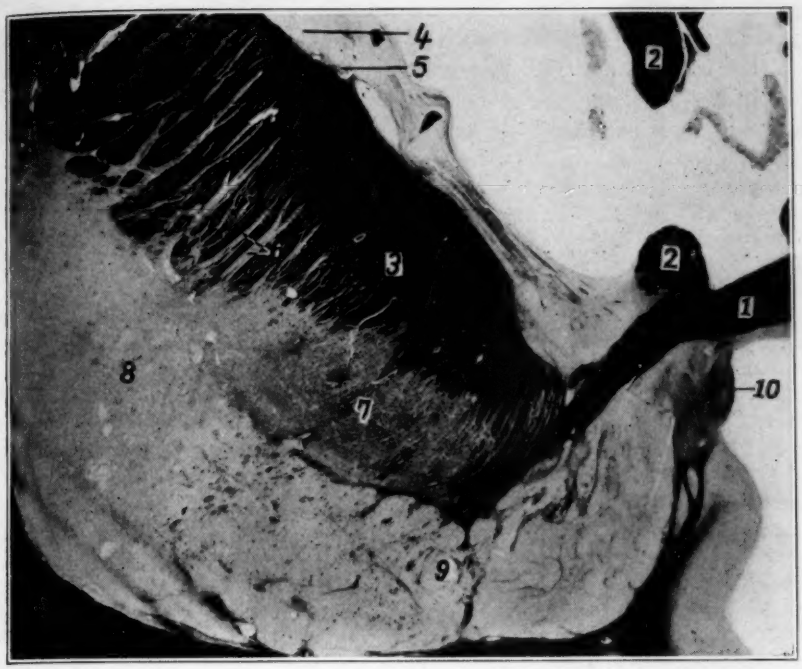

Fig. 2 (section 1,970).—Photograph showing degeneration of fiber bundles in the putamen, the intact "olfactory striatum," and other normal structures at the level of the anterior commissure. The numbers in this and in figures 3 and 4 indicate the following structures:

1, anterior commissure
2, fornix
3, internal capsule
4, caudate nucleus
5, striatum subcaudatum
6, intracapsular striate bands
7, globus pallidus
8, putamen
9, olfactory striatum
10, diagonal band of Broca
11, mamillothalamic tract
12, thalamic fasciculus (H_1)
13, fasciculus lenticularis
14, zona incerta
15, optic tract
16, lamina medullaris externa
17, lamina medullaris interna
18, lamina medullaris limitans
19, ansa lenticularis
20, strionigric fibers (intrapeduncular group)
21, nucleus medialis
22, nucleus ventrolateralis
23, zona reticularis
24, medullary stria
25, nucleus lateralis anterior
26, strionigric fibers (retrolenticular group)
27, subthalamic nucleus of Luys
28, centrum medianum
29, arcuate nucleus
30, subthalamic decussation of Forel
31, substantia nigra, zona reticulata
32, nucleus ruber
33, basis pedunculi
34, substantia nigra, zona compacta
35, fasciculi pontini lateralis
36, lateral geniculate body
37, optic and auditory radiations
38, medial geniculate body
39, medial lemniscus and spinothalamic tract
40, habenula
41, pulvinar thalami
42, tegmental radiations
43, oculomotor nerve
44, dorsal trigeminal tract

putamen and the caudate nucleus, the medullary laminae in relation to the pallidum and the fiber bundles (ansa lenticularis and fasciculus lenticularis) leaving the globus pallidus and connecting it with the red nucleus, the subthalamic nucleus, the nucleus of Forel's field, the interstitial nucleus, the nucleus of Darkschewitsch and the inferior olives.

The well known structures of the corpus striatum as they appeared in the brain of Maynard Shipley are illustrated in figure 3 *A*. Microscopic examination of this region of the brain stem revealed additional neural parenchyma affected by the vascular pathologic changes previously noted. The malacia of the putamen was apparent. On each side the lateral lenticulostriate arteries were evidently involved by the sclerosis, with the result that degeneration of the striatum was present bilaterally. The pallidum was not involved on either side. The caudate nuclei were severely affected at oral levels, and the left was reduced in size. The left putamen was amyelinic and extensively vacuolated in its oral part. It contained partly degenerated fibers throughout most of its extent (figs. 2 and 3 *A*). The right putamen was severely affected in places but was normal in others. On the whole it was less affected than the left. All the vascular pathologic involvement, however, was sharply localized in the caudate nucleus and the putamen on both sides. Throughout its extent the globus pallidus of each side was normal and contained no evidence of focal disease or of degeneration in its efferent tracts.

Two degenerations of fiber tracts could be traced in this brain that are of sufficient interest to merit detailed description. The degeneration in the corpus striatum revealed certain fiber relations between these nuclei and others included in the extrapyramidal system. Of particular note were the fiber connections between the striatum (caudate nucleus and putamen) and the substantia nigra, which have not hitherto been clearly described. The second degeneration concerned cortical projections from the precentral lesion to the arcuate nucleus and the centrum medianum of the dorsal thalamus.

STRIONIGRIC FIBERS

The putamen and the caudate nucleus, although separated by the internal capsule, were connected by numerous bands of cellular and fibrous material (fig. 2). At oral levels the bands were predominantly cellular, but at lower levels degenerated fiber bundles arched laterally through the internal capsule to connect the two nuclei (fig. 3 *A*). Fasciculi of caudate origin gathered first between the nucleus and the internal capsule. They passed through the internal capsule and the dorsal part of the putamen to reach the external medullary lamina of the pallidum. In this lamina many bundles coursed caudally, apparently to end as striopallidal fibers. A large group, however, shifted medially between the internal capsule and the dorsal margin of the pallidum and was destined to end in the substantia nigra. These bundles retained their position in the lateral part of the limiting medullary lamina (fig. 3 *A*) until at more caudal levels the darkly stained fibers which formed the fasciculus lenticularis gathered directly ventral to them. When they were followed downward in the series, both fiber groups were observed to shift medially as they rose through the peduncle and were soon dispersed throughout the width of the peduncle (fig. 4 *A*). The darkly stained pallidal fibers passed dorsally through the degenerated striate fibers (fig. 3 *B*) before emerging from the peduncle to form the fasciculus lenticularis and the capsule of the subthalamic nucleus. There was a sharp separation between the two

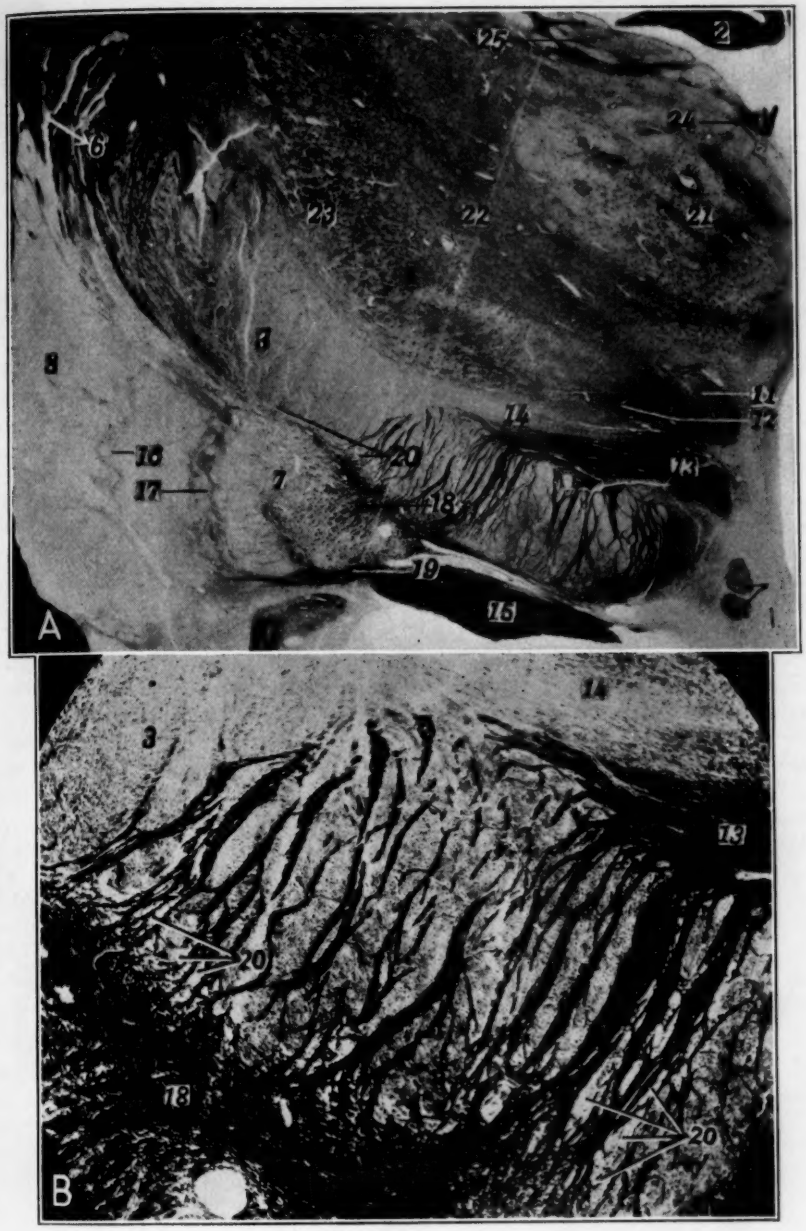

Fig. 3.—*A*, section 1,656, photograph showing malacia in the left putamen, the partly degenerated external medullary lamina of the pallidum and the normal ansa lenticularis, fasciculus lenticularis and thalamic fasciculus. The dorsal thalamus is normal. *B*, enlargement of part of the section illustrated in *A*, showing the position of the degenerated strionigric fibers, which form an irregular stratum between the limiting medullary lamina and the internal capsule. The fasciculus lenticularis rises dorsally through the peduncle.

groups beyond this point. The normal pallidal fibers all passed dorsal to the peduncle, while the degenerated striatal fibers continued caudally in the peduncle to enter the oral end of the substantia nigra (pars reticulata), in which they terminated.

The degenerated bundles from the putamen could not be followed separately from those of caudate origin. The fasciculi from the putamen converged toward the external medullary lamina, turned caudally and as smaller bundles infiltrated the outer segment of the globus pallidus. These striofugal fibers, as in the case of those from the caudate nucleus, could be traced into two localities, some ending in the pallidum while others reached the zona reticulata of the substantia nigra. Some of this strionigric group appeared to join those of caudate origin and to enter the substantia nigra with them, as previously described. Others coursed caudally and accumulated in the ventral part of the globus pallidus and in the external medullary lamina. At still lower levels these fibers constituted the bulk of the lentiform nucleus. Many of them rose through the cerebral peduncle to enter the substantia nigra in the neighborhood of the lateral corticobulbar bundles. Figure 4 *A* illustrates the most caudal group that appears at this level as a degenerated area dorsolateral to the optic tract. Farther caudally (fig. 4 *B*) as the lateral geniculate body appeared, this bundle migrated dorsally around the end of the basis pedunculi to enter the lateral end of the substantia nigra. When the substantia nigra ended at the level of the foramen caecum of the pons, the basis pedunculi was entirely free from degenerated fibers.

In general, the head of the caudate nucleus was connected with the oral and medial parts of the substantia nigra, while the putamen was more closely related to the caudal and lateral parts. In all cases the fibers from the striatum appeared to enter and end in the reticular, or diffuse, part of the substantia nigra.

In addition to the fibers of striate origin, many bundles of cortical origin rose out of the frontopontile segment of the basis pedunculi to enter the zona reticulata of the substantia nigra. Darkly stained fibers, the origin of which has not been determined, bordered the pars compacta of the substantia nigra dorsally (fig. 4 *B*), in relation to the subthalamus and the tegmentum. Although the zona reticulata was apparently reduced, the zona compacta appeared normal.

The efferent tracts from the pallidum have been the subject of considerable investigation, and the present material offered nothing new regarding their termination. The darkly stained fibers of pallidal origin which formed the bulk of the fasciculus lenticularis, the ansa lenticularis and the pallidosubthalamic tract, contrasted strongly with the degenerated bundles of striate origin.

The evidence clearly indicates that no fibers from the caudate nucleus or from the putamen enter the ansa lenticularis or have a relation other than that of contiguity with the fasciculus lenticularis or the pallidosubthalamic tract. We have seen no evidence in this series to indicate that fibers from the striatum connect with the dorsal thalamus and the zona inserta, as is often stated. Efferent fibers from the striatum appeared, therefore, to be all either striopallidal or strionigric.

Thalamostriatal fibers appeared to be present. Fine, darkly stained fibers accompanied the degenerated radiating fasciculi in both the caudate nucleus and the putamen. They were apparent also in the degenerated bands which traversed the internal capsule. These normal fibers detached themselves from the medullary laminae of the globus pallidus and accompanied the radiating fasciculi into the striatum. They were interpreted as afferent fibers to the striatum, most of them coming from the dorsal thalamus. They were distinct in regions where striofugal bundles were clearly degenerated and were absent only in the vacuolated areas where retrograde degeneration had apparently taken place.

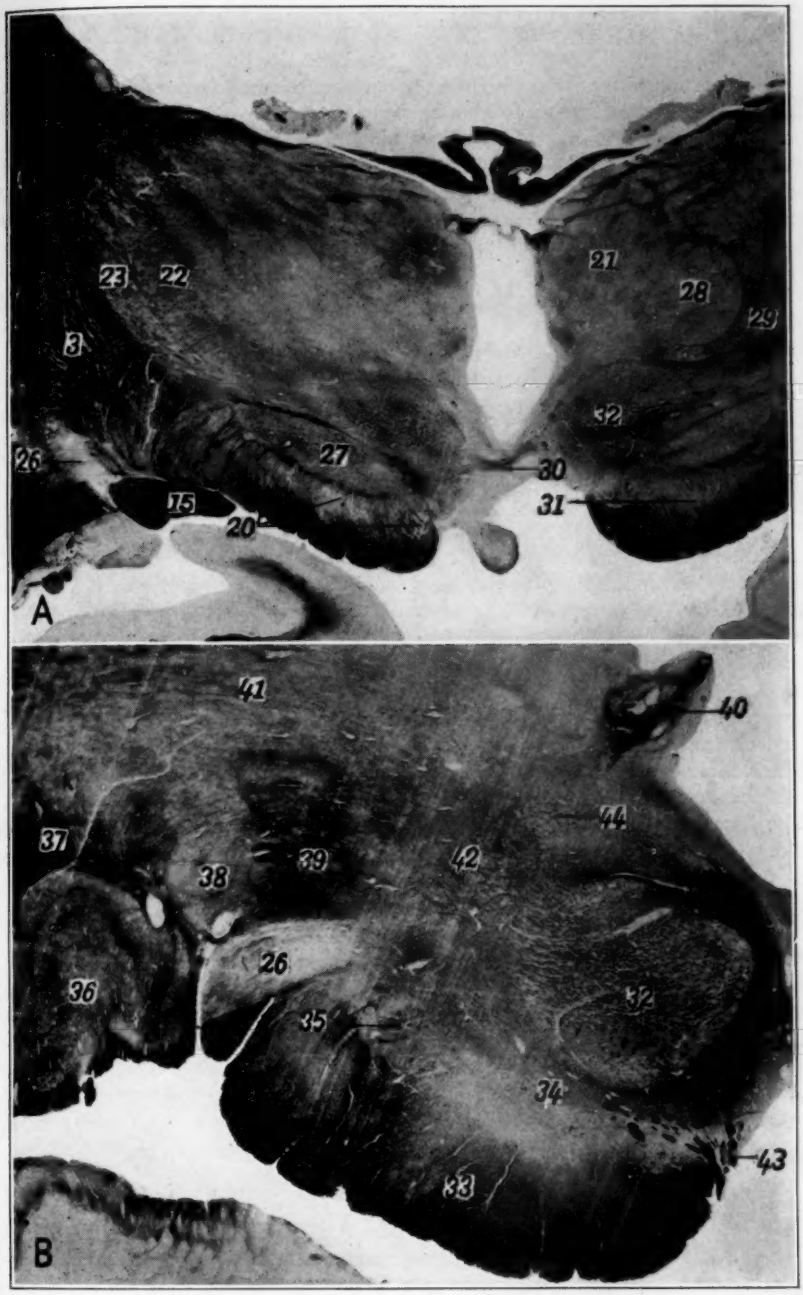

Fig. 4.—*A*, section 1,539. The left side is slightly in front of the right. Strionigric fibers are scattered throughout the left peduncle, and the retrolenticular group appears dorsolateral to the optic tract. The strionigric fibers enter the most cephalic part of the substantia nigra appearing on the right. The fiber degeneration in the left side of the dorsal thalamus is shown. The laminae normally bounding the centrum medianum and the arcuate nuclei laterally are almost absent. *B*, section 1,369, photograph showing the most caudal group of strionigric fibers swinging around the peduncle to enter the lateral end of the substantia nigra. All other structures are normal.

The portion of the striatum labeled "olfactory striatum" in figure 2 was normal and showed no degeneration in its fiber connections. Beyond the fact that it seems to be related particularly to the ventral anterior part of the pallidum adjacent to it, we have no evidence as to its fiber connections. The thalamic fasciculus appeared normal on both sides. The ansa peduncularis stained densely and contained no degeneration. The components of the inferior thalamic peduncle, lateral to the ansa peduncularis, also stained intensely and contained no degeneration. These fibers should probably be regarded as thalamopallidal, connecting the anterior and medial nuclei of the thalamus with the pallidum (Sachs [7] and Huber and Crosby [8]). These fibers could be traced caudally for a long distance in the internal medullary lamina of the pallidum although they had reached this structure at oral levels. Meynert's commissure was normal and contained no degeneration. It was unrelated, therefore, to at least the striate division of the corpus striatum. The bundles of Vicq d'Azyr were moderately demyelinated.

CORTICOTHALAMIC PROJECTION FIBERS

The second fiber degeneration appearing in this series is related to the cortical lesion of the left cerebral hemisphere, which has already been described. It was apparent that the premotor cortex of type 6 was chiefly involved and to a lesser extent that of type 4. The lesion was restricted to the arm, hand and head areas. Figure 4 *A* illustrates the thalamic degeneration consequent to this injury. Reduction in the number of stained fibers on the left side (anterior to the plane of the habenulopeduncular tract and the caudal end of the arcuate nucleus) was apparent. The degeneration extended through the caudal two fifths of the ventral nucleus (pars externa). The most severe degeneration was seen in the laminae which delimited laterally the arcuate nucleus and the centrum medianum. These laminae were normal on the right side but had virtually disappeared on the left. The ascending tracts, the dorsal trigeminal tract, the tegmental radiations, the medial lemniscus, etc., were all normal (fig. 4 *B*) and stained equally well on the two sides. The commissural fibers joining the centrum medianum on one side with that on the other were not degenerated, nor were the periventricular fibers. No vascular pathologic change appeared in any part of the dorsal thalamus. It was concluded, therefore, that the degenerated fibers were cortical projection fibers from the softening in the lower part of the precentral gyrus. We were unable to identify the medial corticobulbar bundles, which also may arise from this area of the cortex, although the lateral group was particularly conspicuous (fig. 4 *B*). Although the cerebral peduncle itself stained darkly, a single large corticopontile bundle within the pons showed definite demyelinization. This was probably a frontopontile bundle from the precentral softening. There was no degeneration in the pyramidal tract on either side.

The connections of the arcuate nucleus and centrum medianum have been discussed in another connection.[9] The main afferent pathways to these nuclei arise from the sensory trigeminal nuclei in the medulla. The arcuate nucleus sends thalamocortical radiations to the precentral

7. Sachs, E.: On the Structure and Functional Relations of the Optic Thalamus, Brain **32**:95-186, 1909.

8. Huber, G. C., and Crosby, E. C.: Somatic and Visceral Connections of the Diencephalon, Arch. Neurol. & Psychiat. **22**:187-229 (Aug.) 1929.

9. Papez, J. W., and Rundles, W.: The Dorsal Trigeminal Tract and the Centre Median Nucleus of Luys, J. Nerv. & Ment. Dis. **85**:509-519, 1937.

gyrus, mainly to the area which in this brain was softened. The centrum medianum in primates and in man does not give rise to thalamocortical radiations. On the basis of this case, however, and of a number of similar ones described by Dejerine,[1] it is probable that this nucleus receives a heavy corticofugal connection from the precentral region. The intrathalamic connections of the centrum medianum and its connections with the corpus striatum were previously described.[9]

COMMENT ON STRIATAL CONNECTIONS

Although a functional duality in the corpus striatum has been recognized by many authors (Hunt, the Vogts, Jakob, and Foix and Nicolesco), the requisite anatomic relationships have been obscure. Many authors have recently expressed the belief that the striatum sends no efferent fibers beyond the pallidum (Wilson, the Vogts, Spiegel,[10] Jakob, Winkler[11] and others). Other investigators have stated that it does, but they did not separate strio-efferent and pallido-efferent fibers as regards their connections to other subthalamic centers. Hunt[4] expressed the opinion that the giant cells of the striatum are part of the general pallido-efferent system and of the same functional import. Dejerine,[1] Grünstein,[12] Foix and Nicolesco[6] and Mingazzini[13] described strio-efferent fibers as contributing to the ansa lenticularis, fasciculus lenticularis and other tracts. From this it seems that the striatum and the pallidum are closely connected and overlap, in spite of a recognized functional duality. But, as we have shown, the interconnections of the striatum and the pallidum are by no means as complete as has hitherto been assumed. An actual duality of connections exists, since the striatum also sends fibers to the substantia nigra.

The radiating fasciculi of the putamen and the caudate nucleus, in particular their efferent fibers, seem to be stained somewhat selectively in many Weigert series of adult brains and are distinguished by a paler or a brown coloration. That they are mainly striofugal was shown first by Grünstein and Wilson. After small lesions in the putamen Wilson observed that "pencils" of fibers degenerate medially into the medullary laminae of the pallidum. The less numerous fibers in these

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10. Spiegel, E.: Die Kerne im Vorderhirn der Säuger, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **12**:418-497, 1919.

11. Winkler, C.: L'anatomie du système nerveux: Le corps strié et le diencéphale, Haarlem, de Erven F. Bohn, 1933, vol. 1, pt. 5; Opera omnia, Haarlem, de Erven F. Bohn, 1929, vol. 9.

12. Grünstein, A. M.: Zur Frage von den Leitungsbahnen des Corpus striatum, Neurol. Centralbl. **30**:659-665, 1911.

13. Mingazzini, G.: Das Mittelhirn, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, pt. 1.

radiating fasciculi which degenerate in the opposite direction and which Wilson described as intrastriate probably correspond to the normal fibers in our series which distribute into the striatum from the medullary laminae of the pallidum. We have interpreted them as afferent fibers to the striatum. Poliak [14] illustrated the polarity of these fibers in his recent monograph (figs. 46 to 50).

The course of these fiber groups through the pallidum has already been described. Many authors, as stated, have expressed the belief that they all end here. Dejerine and Foix and Nicolesco included fibers from the striatum in the efferent pallidal systems and described direct striothalamic connections. The striate fibers joining the fasciculus lenticularis, as described by Foix and Nicolesco, markedly resemble the degenerated strionigric fibers in the ventral part of this fasciculus in our series. Their *faisceau pallidal de la pointe* is clearly identical with the retrolenticular strionigric group described in this paper, which is caudal to the pallidum and swings dorsally around the basis pedunculi to enter the lateral end of the substantia nigra.

Foix and Nicolesco did not recognize this as a direct fiber connection between the striatum and the substantia nigra. We have not observed the fibers described by them as striatal connections with the hypothalamus or fibers of striate origin that join the ansa lenticularis.

After experimental lesions in the putamen Wilson did not observe degeneration beyond the pallidum. This result may have been due to the small size of the lesions in this nucleus. When his lesions involved strionigric fibers in their intrapallidal course, as we have described them, he observed connections with the substantia nigra similar to those described here.

Nearly all investigators have described fiber connections between the corpus striatum (pallidum) and the substantia nigra. Although it was denied by Dejerine, this relationship has been verified by Wilson, Grünstein, the Vogts, Jakob, Riese,[15] Foix and Nicolesco, Morgan [16] and Winkler.[11] The importance of this connection in the mechanism of the extrapyramidal system has not been generally appreciated.

The presence of strionigric fibers in the basis pedunculi is frequently manifested by their paler or brown coloration after Weigert staining, just as the same criterion is useful for distinguishing them in the striatum itself or in the pallidum. Winkler in particular described them in several places as *bandes grises*, or cellular and fibrous bands, which

14. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California, 1932.

15. Riese, W.: Beiträge zur Faseranatomie der Stammganglien, J. f. Psychol. u. Neurol. **31**:81-122, 1924.

16. Morgan, L. O.: The Corpus Striatum, Arch. Neurol. & Psychiat. **18**:495-549 (Oct.) 1927.

extend from the medial segments of the pallidum to the substantia nigra. Although there is a continuation of the zona reticulata of the substantia nigra cephalad in the peduncle, perhaps as far as the pallidum, these *bandes grises* do not contain cells of the pallidal type or cells belonging to the zona compacta of the substantia nigra in primates and in man (Malone [17] and Papez and Aronson [18]). The identification of these *bandes grises* as strionigric fibers either lightly stained or degenerated and corresponding to the group rising dorsally through the peduncle in this series cannot reasonably be doubted.

The most posterior group of strionigric fibers has been demonstrated in experimental studies, in pathologic cases and apparently in myelinization preparations. By other authors it has been considered as a pallidonigric connection. They have used myelinization preparations of fetuses of various ages and of young infants to illustrate the fiber connections of the corpus striatum. The myelinization process in the pallidum (paleostriatum) is usually stated to precede that in the striatum (neostriatum). Winkler,[11] however, has recently described the myelinization process of the corpus striatum as exhibiting rather an occipitofrontal sequence, involving the caudal end of the putamen and the globus pallidus simultaneously. Since much of the striatum lies ahead of the pallidum, there remains a difference in the time of myelinization of the two divisions of the corpus striatum considered as a whole. Winkler has described a tract similar to our retrolenticular group of strionigric fibers in a fetus shortly before term. The tract may originate from the caudal end of the putamen rather than from the pallidum. It appears to us that since the bulk of the efferent fibers from the striatum myelinate later, much of the system is not apparent at this time. This general delay in the myelinization of the fibers from the striatum would be associated with the late myelinization of a group of fibers (strionigric) in the lateral end of the basis pedunculi, as described by Dejerine and by Winkler.[19]

In adult brains, particularly in pathologic cases in which massive lesions have occurred, the most caudal group of strionigric fibers may easily be confused with neighboring fiber systems, i. e., temporopontile projection fibers, lateral corticobulbar bundles (fasciculi pontini lateralis) and, possibly, descending tracts from the subthalamic nucleus, the pallidum or the substantia nigra itself. The lateral pontile fasciculi seem in this series to be entirely of cortical origin and can be followed

17. Malone, E.: Ueber die Kerne des menschlichen Diencephalon, Abhandl. d. köngl. preuss., Akad. d. Wissensch. Phys.-math. Kl., 1910, pp. 1-32.

18. Papez, J. W., and Aronson, L. R.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: I. Ventral Thalamus, Arch. Neurol. & Psychiat. **32**:1-26 (July) 1934.

19. Winkler, C.: Opera omnia. Haarlem, de Erven F. Bohn, 1927, vol. 8; 1921, vol. **7**.

through the substantia nigra into the midbrain and into the medulla. The densely stained fiber groups dorsal to the substantia nigra and lateral to the red nucleus (fig. 4*B*) may include descending tracts from extrapyramidal centers. Whatever the character of these bundles may be, they are all distinctly separate from the strionigric bundles described here. There is no evidence that any of the fibers of striate origin pass beyond the substantia nigra or rise dorsally into the tegmentum, as do the cortical fibers.

Fiber connections from the cortex to the substantia nigra and from the corpus striatum to the substantia nigra are discussed in other connections by many of the authors referred to. Riese, in particular, has discussed the relation between the corpus striatum and the substantia nigra. Although he followed the Vogts as regards the fiber connections of the extrapyramidal system, he cited interesting circumstantial and experimental evidence in support of the striogenic connections as described in this paper.

Clinical investigation of extrapyramidal motor disturbances has shown that a close anatomic and functional relationship exists between the corpus striatum and the substantia nigra. Lesions in the corpus striatum seem to have almost invariably paralleled pathologic alterations in the substantia nigra. It is evident that the strionigric relationship would be impaired by lesions localized in the striatum or in the substantia nigra or interrupting these fiber connections as they traverse the pallidum.

The striatal syndrome includes chorea, akinetic and hypotonic phenomena and the hypertonic manifestations seen in Parkinson's disease and spastic paralysis. Chorea is usually associated with degeneration of the small ganglion cells of the striatum (Hunt), while degeneration of the large ganglion cells is associated with true paralysis agitans (Jakob). The relation of the two cell types of the striatum to the striopallidal and strionigric projection systems is uncertain. Primary degeneration of the substantia nigra following epidemic encephalitis likewise results in parkinsonian symptoms, and there are few other symptoms characteristic of the striatal syndrome that cannot be found in cases in which the principal involvement is limited to the substantia nigra. According to Jakob, the severe symptoms in such cases are associated with degeneration of the zona compacta of the substantia nigra.

Our observations suggest that symptoms attributed to both the striatum and the substantia nigra may result from degeneration of the nerve cells in either the striatum or the substantia nigra or from the interruption of the strionigric fiber connections described in this paper. Downward connections of the substantia nigra are obscure. Whether or not these symptoms would appear after destruction of such efferent

tracts from the substantia nigra (to the pontile nuclei, the tegmentum, the mesencephalon or whatever centers may be concerned) is unknown.

CONCLUSION

Microscopic examination of a complete series of Pal-Weigert sections through the brain stem of Maynard Shipley revealed bilateral degeneration of the caudate nucleus and the putamen, with preservation of the globus pallidus. It is therefore possible to follow independently the efferent fibers leaving these nuclei. The striatum, including the caudate nucleus and the putamen, has direct fiber connections with the globus pallidus and, what is equally important, also with the substantia nigra. The ansa lenticularis, the fasciculus lenticularis and the pallidosubthalamic tract contain no fibers of striate origin. Symptomatology referable in individual cases to either striatum or to the substantia nigra is explained on the basis of an interruption of this strionigric relationship. Cortical projections to the centrum medianum, and the arcuate nucleus of the dorsal thalamus are described.

Case Reports

CHANGES IN THE SPINAL CORD IN DIABETES MELLITUS

Report of a Case with Autopsy

DONALD E. GRIGGS, M.D., AND CLARENCE W. OLSEN, M.D.,
LOS ANGELES

The neurologic complications of diabetes mellitus present themselves clinically as disturbances of sensory, motor, sphincter and trophic functions. The sensory disturbances are especially distressing to the patients. For example, Fitz [1] found "rheumatic pains" or numbness and tingling to be the chief complaint in 14 per cent of two hundred and forty-nine cases, these symptoms being exceeded only by weakness or loss of weight (in 20 per cent) and urinary symptoms and thirst (in 21 per cent).

Although Kraus,[2] on the basis of clinical evidence, concluded that nearly all the neurologic manifestations of diabetes mellitus are due to lesions in the spinal cord or nerve roots, degenerative changes are in fact more common in the peripheral nerves, the most advanced alterations being in their distal portions. The problem of peripheral neuropathy in diabetes has been thoroughly reviewed by Jordan.[3]

Three syndromes occur which point strongly to involvement of the neuraxis. The syndrome of chronic anterior poliomyelitis is distal muscular atrophy of the upper extremities, with little or no sensory disturbance. The syndrome of tabes dorsalis consists of pains, ataxia, a positive Romberg sign, disturbance of the sphincters, absence of deep reflexes and marked impairment of proprioception. The syndrome of dorsolateral spinal degeneration includes acroparesthesia, ataxia, increase or decrease of deep reflexes, impairment of proprioceptive sense and a positive Babinski sign.

Diabetes not associated with syphilis or pernicious anemia in which changes in the spinal cord are observed at autopsy is rare. In a review of the literature to 1928 Woltman and Wilder [4] found reports of forty-two cases of diabetes in which pathologic examination of the spinal cord and peripheral nerves had been made, and in only twenty of these were changes found in the cord. Since, moreover, these cases were all

From the departments of Medicine and Neurology, College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital.

1. Fitz, Reginald, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, p. 146.

2. Kraus, W. M.: Involvement of the Peripheral Neurons in Diabetes Mellitus, Arch. Neurol. & Psychiat. **7**:202 (Feb.) 1922.

3. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, Arch. Int. Med. **57**:307 (Feb.) 1936.

4. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus, Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929.

reported before the advent of serologic tests for syphilis, one cannot entirely exclude this disease as the cause of the lesion. These authors studied three cases of their own but attributed the minor changes to arteriosclerosis or senility rather than to diabetes.

There have been reported since the review of Woltman and Wilder two additional cases in which involvement of the posterior and lateral funiculi was demonstrated.

In 1928, Czoniczer [5] reported a case with neurologic symptoms pointing to involvement of both the posterior and the lateral funiculi, which appeared soon after the onset of severe diabetes. At first paresthesia, hypesthesia, impaired proprioceptive sense and ataxia were the most prominent symptoms, all of which were limited to the lower extremities. Later, weakness in the lower extremities occurred and was followed by paralysis of the bladder and paresis of the upper extremities. The deep reflexes were active throughout the course of the condition, and a Babinski sign on the right was noted. The Wassermann reactions of the blood and spinal fluid were negative, and there was no anemia. At autopsy marked changes were noted, particularly in the posterior funiculus of the upper cervical region of the spinal cord. The gray substance of the posterior horns and the right lateral funiculus were also affected.

In Reynolds' [6] case, a woman aged 58 had paresthesia and ataxia with hypesthesia and loss of reflexes in the lower extremities eight years after the onset of diabetes. The sense of position was definitely impaired in the toes and fingers. At autopsy, marked changes in the central portions of the columns of Goll were noted, particularly in the cervical segments. A few degenerated fibers were also observed in the outer portions of the posterior funiculus. The walls of the blood vessels showed thickening of their media. Reynolds expressed the belief that the lesion was a systemic disease similar to that of tabes rather than subacute combined degeneration.

The following case came under our observation.

REPORT OF CASE

Unregulated diabetes mellitus of five years' duration in a man 46, progressive loss of weight, weakness and impotence for one year, followed by stiffness in the lower extremities; severe ketosis; rapid development of complete ataxia with complete loss of position sense; death after one month; autopsy revealed pulmonary abscess and confluent bronchopneumonia and degenerative changes in the posterior and lateral funiculi, most marked in the cervical and midthoracic regions of the spinal cord.

History.—An electrician, aged 46, entered the White Memorial Hospital on Nov. 11, 1934, complaining of shortness of breath and general weakness for three or four days; muscle pains, especially in the back and neck, for twenty-four hours and drowsiness for a few hours before entrance. Five years before, he had consulted a physician on account of polyuria and was found to have diabetes mellitus. Since then he had taken irregular and various courses of treatment. In the past year he had noticed sexual impotence and progressive

5. Czoniczer, Gabriel: Ein mit Myelitis funicularis komplizierter Fall von Diabetes, Deutsche Ztschr. f. Nervenh. **104**:286, 1928.

6. Reynolds, R. A.: Zur Frage der diabetischen Tabes, Jahrb. f. Psychiat. u. Neurol. **46**:267 (July 20) 1929.

weakness, with loss of weight amounting to 45 pounds (20.3 Kg.). Two months before entrance to the hospital he had noticed stiffness in the legs and difficulty in climbing stairs. He had had difficulty in walking in the dark for one month. He used alcohol sparingly. The family and the personal history, including the venereal history, were otherwise without significance.

Examination.—The patient walked into the ward and though somewhat dull was able to give a history. He showed evidence both of loss of fat and of ketosis with marked dehydration. The pupils reacted to light and in accommodation. The blood pressure was 105 systolic and 70 diastolic. No deep reflexes were elicited. He had loss of sense of position in the toes, and an equivocal Babinski response was noted on both sides. In all other respects physical examination gave essentially negative results.

A specimen of urine revealed 5 per cent sugar, a trace of albumin, a two plus reaction to tests for acetone and a one plus reaction to tests for diacetic acid, with fine and coarse granular casts. The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters; the sugar content, 307 mg., and the carbon dioxide-combining power, 21 volumes per cent. The blood count showed the hemoglobin content to be 85 per cent, the erythrocyte count 4,200,000 and the leukocyte count 9,000, with 48 per cent polymorphonuclears. The Wassermann reaction of the blood was negative.

Course.—The patient was treated for ketosis and on the following day seemed better, but he still complained of severe pains in the back and neck and numbness of the feet, legs and hands. The pain soon disappeared, but he had increasing difficulty in using his hands and four days after admission was unable to feed himself. It was difficult for him to move his lower extremities. In this period he had several intravenous injections of a solution of sodium chloride and dextrose, and two hypoglycemic reactions occurred, with loss of consciousness.

On November 17 the patient was unable to turn without help. He could move his extremities, but with great difficulty and poor coordination. The legs would get "tangled up" and need "straightening out." The tendon reflexes could not be obtained. A Babinski sign was definitely present on the left. From the level of the clavicles downward there was complete loss of sense of position and vibration, but no marked impairment of any other form of sensation. The spinal fluid pressure was normal; the cell count was 5; the reaction to the test for globulin was positive, and the colloidal gold curve was 00000014431. The Wassermann reaction of the spinal fluid was negative.

Two days later the patient began to complain of paresthesias affecting all of the body except the face. Sensation was poorly localized, and stroking the face resulted in tingling of the toes. On November 25 atrophy of the pectoral and the interosseous muscles was recognized. The atrophy progressed with great rapidity, but no fibrillations were observed. Disturbance of bladder function was conspicuously absent.

Beginning on November 18 there occurred a slight rise in temperature, accompanied by difficulty in breathing and discomfort in the lower right part of the chest. On November 30 the patient had a severe chill, and the cough became productive of foul dark material. The respiratory rate increased to 30 per minute. Roentgenograms of the chest revealed bilateral bronchopneumonia, with pulmonary abscess and pleural effusion on the right. There was little change until a sudden turn for the worse on December 10; he died one day later.

Autopsy.—Postmortem examination, which was performed by Dr. T. S. Kimball and Dr. O. I. Cutler, revealed extensive bilateral bronchopneumonia with a large multilocular abscess in the lower lobe of the right lung. There was also

a large collection of purulent material in the right pleural cavity. The brain and spinal cord were examined by Dr. Cyril B. Courville.

The convolutions of the brain were unusually small, particularly over the dorsolateral surfaces of the frontal lobes (microgyria). The leptomeninges showed a moderate degree of thickening and opacity in this same region. The lateral ventricles were symmetrically and moderately enlarged.

The spinal cord was grossly normal externally. On cross-section, however, clearcut degeneration in the posterior funiculi was evident even to the naked eye, being particularly conspicuous in the cervical and thoracic regions. The affected area was sharply delineated from the posterior gray columns by its pale yellow color and swollen appearance.

Blocks of tissue were taken from the spinal cord in the upper and lower cervical segments, the upper and midthoracic segments and the lumbar and sacral segments, as well as from nerve roots of the cauda equina. Sections were prepared and stained with hematoxylin and eosin, by Herxheimer's method for fat, the cyanin method for tigroid material, the Courville-Krajian method for myelin sheaths, Penfield's combined method for microglia and oligodendroglia and Cajal and Bielschowsky's method for nerve fibers.

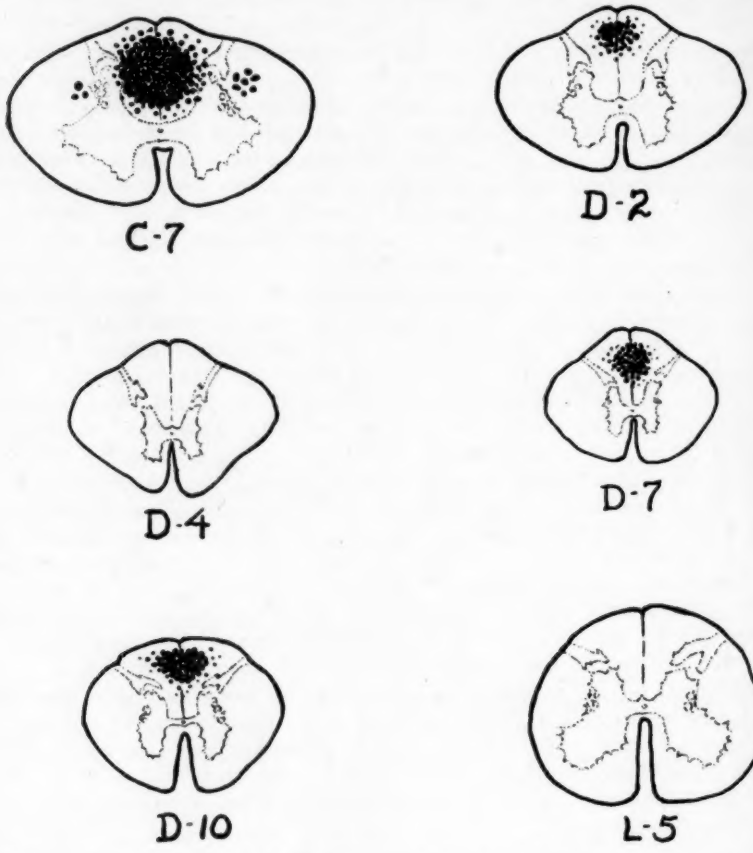
Sections from the cervical region showed almost complete destruction of the posterior funiculi, the limits of the degenerating area extending to the posterior horns on either side. A small margin of normal tissue was preserved along the posterior limit of the posterior funiculi, more on one side than on the other. This area of necrosis had extended laterally, cutting off the medial group of intramedullary dorsal root fibers. The proximal and distal segments of these fibers appeared to be normal, as were the dorsal roots. The degeneration extended over into the lateral funiculi, where it appeared in the form of a vacuolated area with some degeneration of the fibers, as noted in myelin sheath preparations. These changes were more marked on the left side. In the posterior funiculi the necrotic area was occupied by myriads of compound granular corpuscles, which were filled with fat. In the small fragments of tissue remaining in this area there was evidently some increased activity in the formation of new blood vessels, and the myelin sheaths were considerably altered. The remaining axis-cylinders were swollen and distorted, forming small knots in their course.

One rather unusual feature was the occurrence of numerous corpora amylacea in the remaining subpial fragments of tissue in the posterior funiculi and also in the adjoining lateral funiculi. These were particularly numerous along the blood vessels. They were seen only occasionally in the anterior funiculi. These bodies were clearly demonstrated in the hematoxylin and eosin, scarlet red and silver carbonate preparations.

The nerve cells of the posterior column showed loss of chromatic substance in their cytoplasm; many of them had undergone extensive fatty degeneration.

Sections from the fourth thoracic segment showed some edema but no actual necrosis in this region. Sections from the middle thoracic portion of the cord (seventh dorsal segment) showed a second focus of necrosis in the posterior funiculi. This lesion presented the same microscopic appearance as the one previously described but was much less extensive. Sections from the lower thoracic region showed in the various preparations some pallor in the posterior funiculi together with the presence of numerous various-sized vacuolar spaces and again great numbers of corpora amylacea. The myelin sheath preparation showed no gross loss or alteration of nerve sheaths. The cells of the posterior columns appeared to be somewhat paler than usual. The walls of the small arteries in the remaining portions of the posterior funiculi showed a moderate degree of thickening and hyaline change.

Section through the lumbar region also showed great numbers of corpora amylacea around the entire margin of the cord, located particularly in the subpial region and about the blood vessels in the posterior columns. Perivascular round cell infiltration was also observed in the posterior columns, where the tissue again appeared to be slightly vacuolated. There was also definite vacuolation of the periphery of the lateral funiculi, and again the cells of the posterior horn showed loss of tigroid granules and a tendency to fatty degeneration.



Diagrams of sections of the spinal cord showing the extent and location of the lesions.

In the sacral region the corpora amylacea were more numerous than in the thoracic region, but there were no evidences of degeneration either in the posterior or the lateral funiculi, the intramedullary fibers and their sheaths being found intact by specific methods.

In this case there were degenerative lesions of the posterior and lateral funiculi of the spinal cord. The most extensive area of necrosis was in the cervical enlargement; a second was in the middle thoracic segments. Whatever the cause of these changes, it seems evident that the noxious effects of this disease produced necrosis in two or more

local areas in the posterior funiculus. The type and distribution of the lesions distinguish them from those produced by pernicious anemia, in which degeneration is usually most marked in the lower dorsal segments. They differ from the lesion of tabes dorsalis, which is confined to the posterior sensory bundles and is usually most marked in the lumbar segments. Degeneration of the intramedullary fibers of the posterior roots, which is regularly present in tabes, was found only in segments in which the lesion extended into the posterior horn.

Another case similar to the one described has more recently come under our observation.

A 58 year old woman, who had had unregulated diabetes for at least five years, entered the hospital because of cellulitis of the right foot of three weeks' duration. Three months before entrance she had noted numbness and clumsiness in the hands, causing her to drop dishes. This was followed by numbness of the feet and difficulty in keeping her balance, especially when walking at night. Occasionally a sharp pain was experienced in the feet. On examination, the pupils reacted to light; the biceps and triceps reflexes were present, while the patellar and calcaneal reflexes were absent. No pathologic reflexes were elicited. Position sense was absolutely lost in both the fingers and the toes, while movements of the wrist and ankle were correctly interpreted. She was unable to touch her nose or to bring her fingers together while the eyes were closed. Touch seemed normally present, but pain sensation was decreased in both hands and below the knees. In the left foot, which was not swollen, the dorsalis pedis artery could be palpated. The Wassermann reaction of the blood was negative. The marked loss of position sense in the upper extremity seems to indicate a lesion in the posterior funiculi of the cervical region of the spinal cord.

COMMENT

One is led to inquire whether there is any specific and characteristic lesion of the spinal cord due to diabetes; if there is such a lesion, what causes it?

A study of the observations at autopsy shows that in diabetes three types of lesions of the spinal cord may occur.

In the first type changes are to be found in the motor cells of the nuclei of the brain stem and the cells of the anterior horn of the spinal cord. Postmortem studies in the cases of Leichtentritt,[7] Nonne,[8] Bonardi,[9] Findlay[10] and Bramwell[11] revealed degeneration of the cells of the anterior horn and of the bulbar nuclei. Some of the patients

7. Leichtentritt, Heinrich: Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893, p. 32.

8. Nonne, M.: Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lähmung bei Diabetes mellitus, Berl. klin. Wchnschr. **33**:207, 1896.

9. Bonardi, Edoardo: Sclerosi diffusa pseudo-sistematizzata del midolla spinale con polinevrite in un caso di diabete mellito, Morgagni **39**:557, 1897.

10. Findlay, J. W.: Changes in the Peripheral Nerves in a Case of Diabetes Mellitus, Tr. Med.-Chir. Soc. Glasgow **3**:441, 1902.

11. Bramwell, B.: Diabetes; Perforating Ulcer of the Foot; Advanced Atheroma of the Posterior Tibial Artery, the Artery Being Adherent to the Posterior Tibial Nerve, Marked Changes in the Posterior Tibial and Plantar Nerves, Clin. Stud. **5**:279, 1907.

presented in life unmistakable evidence of disease of the lower motor neurons, chronic anterior poliomyelitis. In many cases, however, no clinical evidence, such as weakness or atrophy, was present and the pathologic changes were slight. Whether these changes were primary or were secondary to changes in the peripheral nerves was not always clear. If primary, the possibility of their being due to coincidental progressive muscular atrophy must be given consideration. The relatively high incidence of these manifestations (eight of forty-two cases in the series reviewed by Woltman and Wilder [4]) would suggest that some etiologic relationship exists between them and diabetes.

In the second type there is degeneration of the intramedullary portion of the fibers of the dorsal roots, with consequent secondary degeneration of the posterior funiculi similar to that observed in tabes dorsalis. That there may occur in diabetes mellitus a syndrome clinically suggestive of tabes dorsalis was first mentioned by Althaus.[12] While this syndrome is usually attributed to peripheral neuritis, the illustrated reports of Williamson [13] and Schweiger [14] indicate that in some cases at least the symptomatology has its basis in definite system degeneration. Whether paralysis of the bladder in diabetes is due to interruption of the sensory or the motor elements of the reflex arc is not clear. In a recent report Jordan and Crabtree [15] described several cases of diabetes with retention of urine and suggested that changes in the spinal cord were responsible for the complication.

It is to the third type that we wish to draw particular attention. The lesion in this type is in the posterior funiculi, at times with a minor involvement of the lateral funiculi and the cells in the posterior horns. The area of degeneration does not therefore have a systemic distribution. According to Sandemeyer, Leyden, Goldscheider and Naunyn (quoted by Woltman and Wilder [4]), the changes in the posterior funiculi are similar to those in pernicious anemia. It is to this group that our case belongs.

The pathogenesis of the lesions of the spinal cord in these cases is not settled. Jordan and his co-workers [16] have discussed the many possible causes of neuropathy in diabetes, and they need not be reconsidered here. There are certain aspects of the lesions of the cord which suggest the possibility that they are due to a lowered blood supply, such as would occur in arteriosclerosis. In favor of this concept are the following observations: The changes are of a degenerative nature,

12. Althaus, Julius: On Sclerosis of the Spinal Cord, Including Locomotor Ataxy, Spastic Spinal Paralysis and Other System Diseases of the Spinal Cord: Their Pathology, Symptoms, Diagnosis and Treatment, London, Longmans, Green & Co., 1885, p. 278.

13. Williamson, R. T.: Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus, Brit. M. J. **1**:398, 1894; Changes in the Spinal Cord in Diabetes Mellitus, ibid. **1**:122, 1904.

14. Schweiger, L.: Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **14**:391, 1908.

15. Jordan, W. R., and Crabtree, H. H.: Paralysis of the Bladder in Diabetic Patients, Arch. Int. Med. **55**:17 (Jan.) 1935.

16. Jordan, W. R.; Randall, L. O., and Bloor, W. R.: Neuropathy in Diabetes Mellitus: Lipid Constituents of Nerves Correlated with Clinical Data, Arch. Int. Med. **55**:26 (Jan.) 1935.

such as are produced by ischemia. The lesion is particularly likely to occur in persons who have reached the age when arteriosclerosis occurs, although, to be sure, at least four cases have been reported in which the patient was below the age of 30, one being that of a child aged 9. The most common location of the lesion is in the center of the posterior funiculi of the cervical region, where penetrating arteries are longer than those in any other portion of the spinal cord. It is not likely that there is a gross occlusion of these vessels by thrombosis, but it is possible that a uniform narrowing of the lumens incident to thickening of their walls might be responsible for marked reduction in the blood supply to this region. This reduction in the blood supply may be the sole cause of the degeneration, or it may lower the tissue resistance and so favor the action of other etiologic factors.

The different types of change in the spinal cord in diabetes may possibly be caused by a variation in the etiologic factors involved. For example, a metabolic toxin or avitaminosis may produce degeneration of the intramedullary portion of the posterior roots, causing a system degeneration similar to that of tabes, as illustrated in the cases of Williamson [13] and Schweiger.[14]

Regarding treatment for the changes in the spinal cord in diabetes we have little to offer. In 1929 Angle [17] reported a case of diabetic tabes in which he thought that there was evidence of changes in the posterior funiculi. After a change to a higher carbohydrate and vitamin-rich diet the patient improved. This instance should encourage one to push the protective elements in the diet in such cases. From a preventive point of view a similar program should be followed, as one is as yet uncertain as to the cause of these neurologic lesions.

SUMMARY

The neurologic manifestations in diabetes mellitus are commonly due to changes in the peripheral nerves.

There are, however, cases in which the symptoms are due to definite lesions in the spinal cord. A study of these cases indicates that at least three possibilities exist: (1) degeneration of the motor cells of the brain stem and spinal cord, (2) degeneration of the intramedullary portion of the dorsal root fibers with secondary system degeneration, producing a lesion like tabes dorsalis and (3) funicular necrosis of the posterior columns, occurring especially in the cervical and upper dorsal segments of the spinal cord. This necrosis may extend into the posterior horns and the lateral funiculi in the segments where the lesion is most extensive.

A case of the typical symptoms of involvement of the posterior and lateral portions of the column is reported. The observations at autopsy were those noted under the third type of lesion of the cord. Since these portions of the spinal cord are supplied with blood by the longest penetrating arteries, it is possible that the narrowing of the lumens incident to thickening of the walls of the vessels reduces the blood supply to these regions and produces the characteristic pathologic changes.

17. Angle, F. E.: Tabes Diabetica: Report of Case, U. S. Nav. M. Bull. **26:** 81 (Jan.) 1928.

REPRESSION AND COMMUNICABILITY IN CATATONIC STUPOR

BENJAMIN COHEN, M.D., NORTH GRAFTON, MASS.

The first description of catatonia is credited to Kahlbaum, who in 1874 described a disease picture [1] "in which the patient sits quietly or completely mute and motionless, immovable, with a staring countenance, the eyes fixed on a distant point and apparently completely without volition, without any reaction to sensory impressions, sometimes with a full fledged cerea flexibilitas, as in catalepsy, sometimes with only a slight but definitely appreciable degree of this striking manifestation. The general condition of such a patient gives the impression of a deep mental distress or a fixedness resulting from a severe fright."

The clinical aspects of catatonia have been described in detail by Bleuler [2] and, in recent years, by Hinsie.[3]

In brief, the catatonic patient in stupor is likely to assume peculiar rigid postures, muteness and immobility for periods ranging from months to years. Some repeat the same senseless motions over and over again. Others display strange mannerisms while they eat and walk. Many display a disagreeable feature called negativism: The patient offers stubborn resistance to any attempt to change his attitude and opposes any effort to help him in this regard. He may refuse to dress, eat or move. He frequently evacuates the bladder or rectum on the floor or bed, having previously had opportunity to utilize a proper receptacle but not doing so. The pose and facial expression are often extremely unnatural. There may be marked muscular rigidity. It may be impossible to induce such a patient to walk. A peculiar finding is catalepsy (waxlike flexibility): Although the patient will not move voluntarily, he may maintain fixedly for long periods a position which others make him assume. There may be sudden outbursts of excitement attended by assault, destructiveness and incoherence of speech. The habits are frequently filthy; feces and urine may be taken as food; masturbation may be carried on with open abandon. The lips, eyelids and extremities may become deeply cyanosed, in association with inactivity and immobility.

From the Grafton State Hospital.

Read at a meeting of the Worcester District Medical Society, Nov. 13, 1935.

Granted one of the awards for research in psychiatry by the New England Society of Psychiatry at the Annual Meeting, April 22, 1936.

1. May, James V.: The Dementia Præcox-Schizophrenia Problem, Am. J. Psychiat. **11**:405-407 (Nov.) 1931.

2. Bleuler, Eugen: Textbook of Psychiatry, translated by A. A. Brill, New York, The Macmillan Company, 1924, pp. 403-410.

3. Hinsie, Leland E.: Clinical Manifestations of the Catatonic Form of Dementia Praecox, Psychiatric Quart. **6**:469-471 (July) 1932.

From the questioning of several patients who have emerged from this peculiar state, I have reason to believe that they did not have voluntary control of their behavior during stupor.

THERAPEUTIC ATTEMPTS TO ABOLISH STUPOR

In recent years several articles have appeared describing two methods of dissolving catatonic repression and effecting temporary communicability: (1) inhalations of carbon dioxide and oxygen [4] and (2) the intravenous injection of sodium amytal.[5]

Although there has been some variation of technic, the first method consists basically of the administration of a mixture of 40 per cent carbon dioxide and 60 per cent oxygen by inhalation for one or two minutes. Then the patient is allowed to breathe ordinary air. The respiration shows increase in depth and intensity; sometimes cyanosis appears. There may be muscular twitching or convulsive movements. The face may assume an expression of amazement or intense horror. For from fifteen to twenty-five minutes the patient may experience a lucid period, during which he may answer questions. Then he reverts to the original state. The effect of the gas is not uniform. Some patients show little or no response or speak in an unintelligible fashion. Observers have noted improvement in certain patients who have repeatedly undergone this treatment; other patients have demonstrated little benefit.

Sodium amytal (sodium iso-amylethylbarbiturate) has been given intravenously in a dilution of from ¾ to 1½ grains (48.5 to 97 mg.) per cubic centimeter of distilled water, at a rate not faster than 1 cc. a minute. The patient first experiences ataxia, nystagmus, defects in speech, fatigue, dizziness and blurring of vision. Within a few minutes he may become drowsy or euphoric. The effect is variable. Some mute patients may answer questions relevantly and coherently during the prenarcotic period. Others may cry, express delusions or respond in evasive fashion or reluctantly in monosyllables. Injections of from 7½ to 9½ grains (486 to 615 mg.), and more infrequently up to 15 grains (972

4. (*a*) Solomon, H. C.; Kaufman, M. R., and D'Elseaux, F.: Some Effects of the Inhalation of Carbon Dioxide and Oxygen, and of Intravenous Sodium Amytal in Certain Neuropsychiatric Conditions, Am. J. Psychiat. **10**:761-769 (March) 1931. (*b*) Langenstrass, Karl H.: Treatment of Stupor, ibid. **11**:447-455 (Nov.) 1931. (*c*) Kelman, Harold: Observations in Catatonia with Mixtures of Carbon Dioxide and Oxygen, Psychiatric Quart. **6**:513-522 (July) 1932.

5. Harris, Meyer M., and Katz, Siegfried E.: Effect of the Administration of Sodium Amytal and Sodium Rhodanate on Mental Patients, Am. J. Psychiat. **12**:1065-1083 (March) 1933. Lorenz, W. F.: Some Observations in Catatonia, Psychiatric Quart. **4**:95-102, 1930. Lorenz, W. F.; Reese, H. H., and Washburne, Annette C.: Physiological Observations During Intravenous Sodium Amytal Medications: Preliminary Report, Am. J. Psychiat. **13**:1206-1212 (May) 1934. Lindemann, Erich: Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, ibid. **11**:1083-1091 (May) 1932. Smith, P. L., and Schwartz, D. K.: Sodium Amytal as a Means of Obtaining Contact in Stuporous and Uncommunicative Cases: Preliminary Report, Psychiatric Quart. **8**:748-753 (Oct.) 1934. Solomon, Kaufman and D'Elseaux.[4a]

mg.), produce narcosis, with disappearance of the corneal reflex. Communicability in some cases may be evoked with much smaller doses. Toxic features, mainly of respiratory character, such as irregularity of breathing, cyanosis and cessation of respiration, are considered to be due to too rapid injection of the drug. Repeated treatments have been attended by improvement in some cases; however, there is no constancy of effect.

SITUATIONS MODIFYING CATATONIC REPRESSION

I have been concerned mainly with the clinical aspects of catatonic stupor and the ways of modifying repression without the use of drugs. The circumstances under which several resistive, mute patients with catatonia gave up repression are of interest:

When an attempt is made to walk with a patient suffering from typical catatonia considerable resistance is offered, but if the assisting person is determined the patient walks progressively better, sometimes surrendering mannerisms of gait as the speed of walking is increased, perhaps smiling at times or answering a question addressed at the time. The respiratory and circulatory systems become physiologically stimulated, reflecting such changes by increase in the pulse rate and the depth and frequency of respiration. Some analogy to the effect of carbon dioxide and oxygen may exist here.

A stiff, immobile patient, apparently oblivious to all, may suddenly bring up her hands to arrest the rapid passage of a cup, sent coursing toward her on an abruptly tilted tray. On one occasion a comment that an item of food on her tray might benefit her caused such a patient immediately to abandon eating and turn her plate so that the vegetable mentioned faced her; she then plunged her spoon into it. On the other hand, the remark of the physician that she would some day be restored to the community caused her to show intense rage, grit her teeth and hurl a defiant "No!"

Candy or gum held before an extremely resistive patient with catatonia frequently evokes a broad grin and the opening of the mouth or the proffering of the hand for the item presented.

The touching of a painful area, such as a gingival abscess or an ulcer on the leg, or the persistent offering of a drug may evoke spontaneous complaint or an answer to a question simultaneously asked. Spilled food or a fly may be spontaneously brushed away.

On one occasion a denudative, rigid woman pulled up her bed sheet to cover an exposed pubis as a male physician passed her bed.

A challenge directed to a man with catatonia that he could not turn his averted head to meet the eyes of the physician brought the desired response. Although a patient may violently resist any effort to be moved, there are quick retreat and rapid return without help to the place from which the patient was taken.

Prolonged conversational methods alone evoked fairly relevant and coherent speech on the part of two lordly patients who had been mute for long periods.

One patient would eat only when he was permitted to eat alone in a room. If any one entered eating immediately ceased. When he emerged from stupor he explained that the presence of others made him feel that

he had done wrong and that he was eating food taken away from others. Hence, he averted his head or let it fall on his chest. Utilization of such information may make it unnecessary to feed similar patients forcibly.

Plantar stroking may produce anticipatory retraction of the foot as the examiner's hand is brought again near the patient's foot.

WRITING AS A METHOD OF EFFECTING COMMUNICABILITY

My observations have been specifically focused on the influence of writing on patients with catatonia. The spontaneous writing of these patients, if they write at all, is an irrelevant, meaningless jumble of real or coined words. I have endeavored to use therapeutically a directed form of writing.

Some patients with catatonia spurn a pencil when it is offered; a few may accept it. Further attempts may condition a response. After repeated trials the patient may come to accept it without hesitation. A few write their names on initial direction, when they are not communicative otherwise. Others at first must have the hand guided to write their names or other expressions, and when so started they may continue without direct aid.

Despite the imperfections of spontaneous composition, some patients with catatonia will take dictation with progressively improving accuracy, occasionally omitting a word and at times introducing an expression of their own. Penmanship, despite years of disuse, is generally good and easily legible. Errors of spelling, which are seen, are consistent with the extent of the patient's education.

Dulling of attention may reveal itself by uncrossed t's and undotted i's and by omission of apostrophes, capitals and punctuation.

The more easily persuaded patients utilize corrections; an obstinate patient, however, perseveres in recording his error, despite frequent erasing by the physician.

An occasional hitherto mute patient will tire of writing and answer verbally, or will first break silence by a remark of this nature: "How do you spell 'vowels' (a dictated word)?"—"Funny writing, isn't it?"—"I'd rather not write but talk," etc.

I have noted a patient who, when she began to speak, found it best first to write her answer and then read it, a strange transitional stage. A few broke silence on direction by reading what had been written in response to dictation.

A patient with catatonia, though slow to accept a pencil, returns it rapidly and sometimes places it in a designated hand or pocket. When a pencil is dropped by the physician, as though by accident, the patient may sometimes be persuaded to pick it up.

Some patients in giving answers are likely to write: "I don't know." In severe cases I have reason to know that this ignorance was apparent and not real. I demonstrate this by writing every alternate letter in the name of the hospital, the physician's name and the month, leaving blanks between, which the patient is requested to fill. Several patients proved able to do this correctly. When a married patient denies wedlock I am likely to ignore such an answer and direct the patient to write the name of the marital partner. A patient who professed ignorance of the names

of her parents found it easy to tell the physician correctly that they were George and Mary when he ventured the statement that they were called Jonathan and Edith. The same patient admitted ability to answer many questions to which she customarily replied: "I don't know."

THERAPEUTIC INTIMATIONS

In several cases writing has served satisfactorily as an entering wedge and has spurred the patient to increased endeavor in other respects, mainly of an occupational nature.

By citing a number of representative cases I can perhaps demonstrate some of the more immediate effects of the method described.

REPORTS OF CASES

CASE 1.—E. W., a woman aged 32, with muteness, peculiar mannerisms and stiffness of at least one year's duration, when examined at the Grafton State Hospital, was tidy but uncommunicative and kept her face concealed and the head averted when brought into the room. She maintained a peculiar facial grimace, and when questioned in ordinary fashion she did not reply. However, she raised each arm when requested to do so and even answered simple problems in arithmetic with her fingers. She was given paper and pencil and was asked to write the answers. She named the hospital and gave the date, the date of her birth, etc., correctly. Then she tired of writing and began to speak in an audible, unnatural whisper. Her voice gradually became stronger, and she no longer found it necessary to write. She admitted various visual hallucinations, identified the examiner and showed partial retention of school knowledge. She complied with various directions. When she came to the staff meeting, however, she was guided into the room, with her eyes closed. She obeyed simple commands and answered many questions on paper but refused to speak. Treatment was resumed in the ward. She was found able to execute various instructions and to transmit messages verbally from the physician to the nurse. On one occasion she was asked if the physician was her friend. She wrote: "Yes." When asked if she was the physician's friend, she wrote: "No!" Asked what she would like to do, she wrote: "Nothing." However, on direction she did a certain amount of work, seemingly resenting it and screaming in frenzy, though inconsistently complying without special coercion. The physician was later told that the patient cooperated only when he was about, thereafter reverting to the original stuporous state. The patient was informed that in the absence of the physician she should heed the nurse. Compliance slowly improved. She learned to talk more relevantly and freely. Cooperation improved. She was often found reading magazines and became capable of a certain measure of useful occupational endeavor.

CASE 2.—A. L. P., a woman aged 25, who had been in a catatonic stupor for five months, had a long history of sexual delinquency and had had several illegitimate pregnancies. Strangely, she had prophesied her stupor, once having said that she was taught in catechism that pride, covetousness, gluttony, anger and other sins, unless repented, deaden the senses. She believed that she had committed an unforgivable sin and that at confession she had omitted to tell of one sin and so could not be forgiven. She felt that she was in a "terrible condition" as far as the salvation of her soul was concerned and stated: "It is a flame burning in me." She went through a month of extreme excitement and resistiveness. She then became mute and denudative. She was fed with a tube, and large amounts of bromides and barbiturates were given in an effort to control her. She

lapsed into apparent depression and stupor. Her body became stiffly fixed, and she peered fixedly into the distance at light until severe conjunctivitis resulted. Blindfolding and care in bed finally became necessary. At times she fixed her head stiffly; her eyeballs rolled high into the sockets, and the eyelids quivered.

On the first day of the approach by writing a pencil was placed in her hand. Although about seven times her hand was guided by the physician to write her name, she would not write it once herself. Then she spontaneously made dense masses of circles on paper and wrote the word "garanium." When told that the word had not been spelled correctly she wrote: "Spells gerranium." She readily relinquished the pencil on direction.

On the second day she seemed much the same; that is, she lay flexed in bed, with staring expression and the pupils markedly dilated. There was no compliance at first; then she wrote her name, the place of her birth and the names of her parents. The physician dictated some encouraging material, which she recorded accurately. She did not talk, but when she was asked to nod her head when the name of the nurse was mentioned among a multitude of names she did so. The nurse asked her: "How are you?" The patient wrote: "Fine, how are you?" In answer to the question: "Are you better?" she wrote: "Yes, I am very much better." When asked if she were willing to get dressed, she clapped her hands gleefully, got out of bed, dressed herself and subsequently passed objects on direction and pushed a floor swab about. She waved a cheery farewell when the physician left. On the next day she complied with directions relative to getting out of bed, dressing, etc. Her expression was sensible and friendly. She followed verbal directions and was willing to answer questions. On the fourth day she was found reading a religious journal and on request read passages aloud. On the same day she helped to serve food to other patients.

In the next month her weight, which had been 90 pounds (40.8 Kg.), increased 8 pounds (3.6 Kg.) and still more in the succeeding six months, with a total gain of 40 pounds (18.1 Kg.). It still remained at approximately that level at the time of writing. It became possible for her to do work and attend entertainments. She subsequently underwent a relapse, possibly in consequence of premature cessation of writing procedures. She reverted to a condition of untidiness, occasional violence and partial stupor, from which she could be aroused by writing. Silliness, admitted hallucinations and facetiousness in part opposed treatment. Recent examination indicated that the patient was still able to take dictation in a good hand and with fair accuracy; this procedure will be continued.

Case 3.—A. S., a woman aged 32, who had been in a catatonic stupor for five months, was admitted to the Grafton State Hospital from the Boston Psychopathic Hospital, with a history of restlessness, resistiveness, unwillingness to eat and muteness for about a week. At the Boston Psychopathic Hospital the administration of 4½ grains (292 mg.) of sodium amytal intravenously caused the patient to answer various questions concerning events in the distant, but not recent, past. She received 1½ grains (97 mg.) more but became too stuporous to answer further questions. In this hospital she was mute and sat in a constrained attitude, staring straight ahead. She was negativistic, maintained one position constantly and was apathetic and untidy in appearance. She was reluctant to eat and had to be fed with a spoon; on several occasions feeding with a tube was necessary. She continued immobile and resistive; finally, care in bed became necessary. After about five months of such behavior an experimental approach by writing was attempted. First, however, several questions, including a request for her name, were addressed to her orally. As expected, she did not answer. A pencil was placed in her

hand and a notebook in her lap. She was asked to write her name and did so. Dictation was tried, and she wrote readily and correctly. The physician asked if she wanted some milk and directed her to write her answer. She wrote: "No." He then dictated: "Yes, I want a glass of milk," and she wrote it. Milk was brought, and she drank it without urging. The physician remarked that a few drops remained, and she raised the glass to her lips to drain it to the bottom. A note dated four days later stated that the patient did not require supervision while eating. At times she was disposed to negativism and wrote: "No." But when she did so, she was instructed to write: "Yes, I will have ————" or "I will do————," and there was compliance thereafter. On the fourth day she did some reading. On the fifth day a deportation warrant was served on her. When questioned by the immigration inspector she nodded certain answers, and on direction she correctly wrote her name and place and date of birth. On the thirteenth day she sat up, ate a regular meal without coercion and went to the lavatory. On the fifteenth and sixteenth days there was evidence of a relapse, and again it was necessary to feed her; she had also become uncommunicative.

It was decided to reattempt what had formerly been done. A pencil was placed in her hand, but she would not take hold of it. Finally, through persistence on the part of the physician, she grasped it. She was directed to write her name but would not do so. The physician guided her hand to write her first name. She was asked to do it herself—there was still no cooperation. Another tangent was attempted. The physician expressed wonder whether or not she could spell words of more than average difficulty. She cooperated with this form of dictation and recorded the following words, misspelling some as indicated: "occassion, vomitted, paraphernalia, extravagence, litter, jetty, illiterate." Constantly, while writing the patient forgot to cross the t's and dot the i's. A single comment in each case prompted correction. The physician then dictated and she recorded material of the following nature: "I have been getting much better, and I look forward to the time when I can leave this institution . . . a normal, sane, healthy person. No one can be healthy without eating," and so on. The physician questioned her: "Do you recognize us as your friends?" She wrote: "Yes." To the question "Are you willing to understand that whatever we advise is in your best interest?" again the answer "yes" was written. To the question "Will you therefore take food voluntarily?" she once more wrote: "Yes." She was given a glass of milk, which she drank to the bottom, without assistance or coaxing. That night she ate supper without aid. On the next day she omitted breakfast, but from that time she accepted regular trays and even extra helpings.

Subsequently, when she had become freely communicative, she was asked: "Why did you start writing and later eating?" She answered: "You told me to do it." She informed me about her experiences during catatonia. She could not explain why she could not eat. She did not resist feedings with the tube because she was unable to do so. There was some amnesia for the stage of excitement of the psychosis. She stated that during the period of stupor she was aware of every one with whom she came in contact. She told how she had once tried to lift a cup to her lips but found herself powerless to do so. On one occasion, during stupor, she was asked by a patient near if the latter might not have some corn bread which she had left untouched on her tray. She wanted to offer it but could not utter a word. During the height of stupor, she related, she was powerless to reply verbally but still retained the ability to respond in writing. After writing her answers for a while, it became possible on some occasions to give verbal replies.

SUMMARY AND CONCLUSION

I have endeavored to describe the clinical nature of catatonic stupor, two chemical methods of effecting communicability, some circumstances under which patients with catatonia surrender repression and evidence which suggests that writing may be of value therapeutically.

It is my observation that in this stubborn disease there is a repression of variable severity and that the method which I have described, much like the two first mentioned, is not applicable in all cases of catatonia.

However, it merits trial since it is uncomplicated, affords certain patients with catatonia a means of expression otherwise not possible to them, is informative, presents no dangerous features and in some cases is directly productive of useful socialization.

By further studies one may obtain a fuller concept of its value and limitations.

SPECIAL ARTICLES

THE CEREBELLUM

A REVIEW AND INTERPRETATION

O. LARSELL, PH.D.
PORTLAND, ORE.

Detailed studies of the comparative anatomic relations and development, phylogenetic and ontogenetic, of the cerebellum in mammals and submammals have thrown new light on the functional connections and relations of its fundamental divisions. They have made necessary a modification of the morphologic interpretation of the organ and some revision of terminology. This reinterpretation has been made gradually in a series of papers, which have been chiefly descriptive. Changes in terminology have been made grudgingly, with a desire to avoid encumbering further an already troublesome nomenclature. As the studies have progressed, some new terms have seemed necessary, and modifications of old terms have also been introduced from time to time. These changes are scattered through a number of papers, for which reason it appears desirable to gather them together into one article, to point out briefly the reasons for their use and to discard some that have been used more or less ambiguously.

A review of some of the principal facts of the comparative anatomic and embryologic development of the cerebellum in relation to the results of experimental anatomic studies of its connections, both internally and with other parts of the nervous system, should be of value. Detailed consideration of the literature is unnecessary because of the recent excellent treatment by Ariëns Kappers, Huber and Crosby.[1] The results of physiologic and clinical investigation will be omitted from consideration, since the purpose of this review, primarily, is to present in broad outlines the evidence for a somewhat modified morphologic conception of the cerebellum. The details of evidence are presented in the papers cited.

From the Anatomical Laboratory, the University of Oregon Medical School.

This research has been aided by a grant to the University of Oregon Medical School from the Rockefeller Foundation.

1. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, vol. 1.

The subdivisions used are based largely on the cerebellum of the opossum, small bats, the mole and the rat. In these forms, owing to the primitive structure or the small size of the animal or to combinations of these factors, the mammalian cerebellum is represented almost in diagrammatic form. A comparison of the cerebellum of these animals with those of a number of other mammals and with descriptions in the literature of many more convinces me that the fundamental mammalian pattern of the organ is presented in the animals named and, of course, in others which I have not studied at first hand.

PRIMARY SUBDIVISIONS

Herrick [2] in 1914, in his study of the urodeles, laid the foundation for a sound morphologic interpretation of the cerebellum. Ariëns Kappers [3] has called attention to the corpus cerebelli and auricular lobe in fishes and other vertebrates. In 1934, in a general paper,[4] I pointed out that in amphibians, reptiles and mammals the cerebellum consists of two fundamental divisions, namely, (1) a vestibulo-auricular (vestibulolateral in aquatic species or stages) or flocculonodular lobe and (2) a predominantly proprioceptive corpus cerebelli (i.e., for muscle sense) (fig. 1 *A* and *B*).

The corpus cerebelli has its origin in the dorsal part of the rostral end of the massive part of the medulla oblongata. The region in which the trigeminal nerve terminates rostrally in the bulb also receives spinocerebellar fibers. There is formed a dorsal commissure connecting the two sides. This is the commissura cerebelli, which contains trigeminal and spinocerebellar fibers. In lower vertebrates direct trigeminal root fibers constitute an important element of the commissure. In higher forms secondary trigeminal fibers, having their origin in a special part of the superior nucleus of the fifth nerve, namely, the nucleus of the commissura cerebelli, appear to replace the direct root fibers of the fifth nerve. The spinocerebellar element of the commissure gradually assumes the ascendancy and in mammals obscures the trigeminal component. The latter, however, is recognizable in lower mammals in its typical relations and probably will be demonstrated by suitable technic in higher mammals also.

The vestibulolateral, or vestibular, part of the cerebellum, the auricular lobe of aquatic vertebrates, also has a commissure connecting the two halves, the commissura lateralis. This is made up primarily of

2. Herrick, C. J.: The Cerebellum of Necturus and Other Urodele Amphibia, J. Comp. Neurol. **24**:1, 1914.

3. Ariëns Kappers, C. U.: Die vergleichende Anatomie der Nervensystems der Wirbeltiere und des Menschen, Haarlem, de Erven F. Bohn, 1920, vol. 2.

4. Larsell, O.: Morphogenesis and Evolution of the Cerebellum, Arch. Neurol. & Psychiat. **31**:373 (Feb.) 1934.

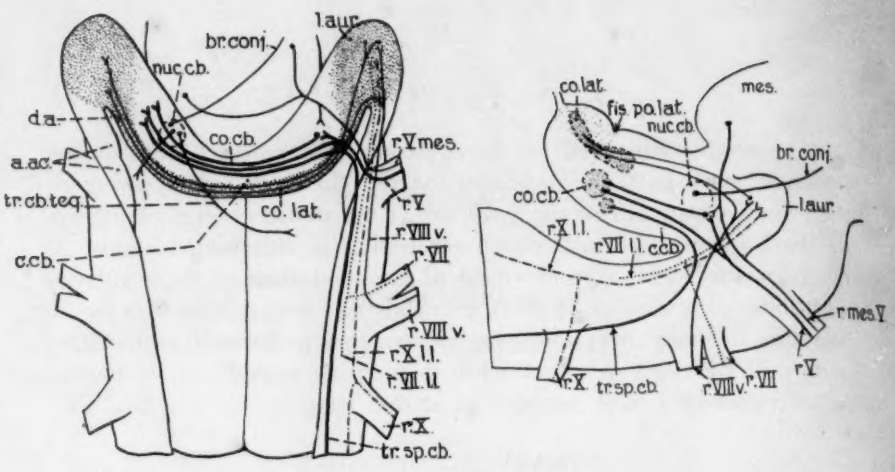


Fig. 1.—Diagram (left) of the cerebellum and its chief connections in Triturus torosus (slightly modified from figure 4, Larsell [4]). Diagram of the cerebellar region and the chief fiber tracts in Triturus as projected on the sagittal plane (slightly modified from figure 5, Larsell [4]). The auricular lobe is stippled in both diagrams.

In this figure and in the accompanying figures, the following abbreviations are used:

a. ac., acousticolateral area
aq. Syl., the aqueduct of Sylvius
br. conj., the brachium conjunctivum
cb. hem., the cerebellar hemisphere
c. c., the central canal
c. cb., the corpus cerebelli
co. cb., the cerebellar commissure
co. lat., the lateral commissure
c. po. b., the pontobulbar body
cr. I., the crus I
cr. II, the crus II
cul., the culmen
d. a., the anterior diverticulum of the fourth ventricle
fasc. unc., the fasciculus uncinatus
fast., the fastigium
fis. pc., the fissura praeculminata
fis. pfl., the parafloccular fissure
fis. ppd., the prepyramidal fissure
fis. pr., the fissura prima
fis. sec., the fissura secunda
fis. po. lat., the posterolateral fissure
floc., the flocculus
l. ant., the anterior lobe of the corpus cerebelli
l. aur., the auricular lobe
l. fl. nod., the flocculonodular lobe
ling., the lingula
lob. ans., the lobulus ansiformis
lob. med. Ing., the medial lobe of Ingvar
lob. po., the posterior lobe of the corpus cerebelli
lob. sim., the lobulus simplex
med. obl., the medulla oblongata
mes., the midbrain
nod., the nodulus
nuc. cb., the nucleus cerebelli
nuc. dent., the nucleus dentatus
nuc. fast., the fastigial nucleus
nuc. int., the nucleus interpositus
nuc. vest., the vestibular nuclei
pfl., the paraflocculus
pl. ch., the choroid plexus
po., the pons
pyr., the pyramis
r. l. v. 4, the lateral recess of the fourth ventricle
r. V, the trigeminal root
r. V mes., the mesencephalic root fibers of the fifth nerve
r. VII, the root of the facial nerve
r. VII l. l., the lateral line root fibers of the seventh nerve
r. VIII v., the vestibular root
r. X, the vagus root
s. in. cr., the intercrural sulcus
tons., the tonsilla
tr. cb. teg., the cerebellar tegmental tract
tr. d. vest., the direct vestibular tract to the cerebellum
tr. vest. cb., the vestibulocerebellar tract
tr. sp. cb., the spinocerebellar tract
tr. sp. cb. d., the dorsal spinocerebellar tract
tr. sp. cb. v., the ventral spinocerebellar tract
tr. trig. cb., the trigeminocerebellar tract
t. v. 4, the taenia of the fourth ventricle
uv., the uvula
v. m. a., the anterior medullary velum
v. 4, the fourth ventricle

direct vestibular root fibers and was described by Johnston [5] in Petromyzon. The details of these two commissures are given in the papers cited and will not be reviewed here. In previous papers I have been uncertain whether vestibular fibers cross in the midplane in reptiles, forming a lateral commissure. Recent study of a considerable range of reptilian material convinces me that there is a true commissure, although small, in these forms also. These two commissures represent the primitive connecting fibers between the bilateral halves of their respective fundamental cerebellar divisions, namely, the corpus cerebelli and the auricular lobe of lower vertebrates, or the flocculonodular lobe of mammals.

FISSURA POSTEROLATERALIS

Between these two fundamental divisions there occurs a fissure, which is constant throughout the vertebrate series. There has been much confusion concerning it because in the adult mammalian cerebellum, which has served as the point of departure for most studies on the organ, this fissure is both reduced in apparent importance as a landmark and subdivided by secondary growth of cerebellar parts. It is present in Triturus and other urodeles (fig. 1 *A*). Although it is obscure in Amblystoma, so that it was not recognized in my earlier studies,[6] reexamination of Amblystoma material shows its presence. It is also observed in reptiles and mammals.[7] I called it the uvulonodular fissure in urodeles and reptiles because it corresponds in part to the mammalian fissure of that name, although neither the uvula nor the nodulus is present in these forms. Subsequently, it seemed better to introduce the new term, fissura posterolateralis, for in mammalian embryos as well as in submammals it extends from one side of the cerebellum to the other, passing over the posterior surface of the organ (figs. 2 and 7). Streeter [8] recognized this continuity in naming it the "sulcus floccularis et postnodularis" in the human embryo (page 68). Ariëns Kappers called the lateral part of the corresponding fissure in fishes the paraauricular fissure. Bradley [9] pictured it (sulcus IV, in his drawings) in

5. Johnston, J. B.: The Brain of Petromyzon, J. Comp. Neurol. **12**:1, 1902.

6. Larsell, O.: The Cerebellum of Amblystoma, J. Comp. Neurol. **31**:259, 1920; The Development of the Cerebellum in Amblystoma, ibid. **54**:357, 1932.

7. Larsell, O.: (*a*) The Cerebellum of Reptiles: Chelonians and Alligator, J. Comp. Neurol. **56**:299, 1932; (*b*) Development and Morphology of Cerebellum in Opossum: I. Early Development, ibid. **63**:65, 1935; (*c*) Development and Morphology of Cerebellum in Opossum: II. Later Development and Adult, ibid. **63**:251, 1936; (*d*) The Cerebellum and Corpus Pontobulbare of the Bat (Myotis), ibid. **64**:275, 1936.

8. Streeter, G. L., in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2.

9. Bradley, O. C.: On the Development and Homology of the Mammalian Cerebellar Fissures, J. Anat. & Physiol. **37**:112, 1903.

various mammals as a continuous fissure. In 1932 I applied the designation sulcus paraflocculari s to the lateral part of the fissure in the young alligator. This term was intended in the same sense as the sulcus para-auricularis of Ariëns Kappers. However, it suggests also a relationship to the paraflocculus, although this structure has not appeared phylogenetically in reptiles and the term was unfortunate. Subsequent studies made it clear that Bolk's "paraflocular sulcus" in mammals is distinct from the floccular sulcus, both developmentally and in adult

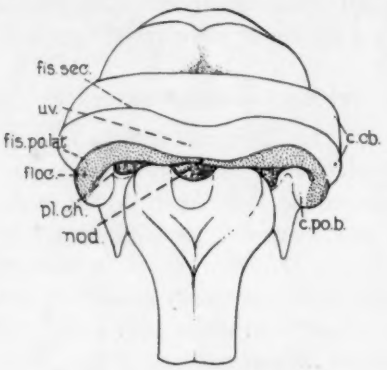


Fig. 2.—Posterior view of the cerebellar region of the bat fetus (Corynorhinus sp.), 14 mm. in crown-rump length (redrawn from figure 8 *A*, Larsell and Dow [17]). In this figure and in all the accompanying figures except figure 6, the flocculonodular lobe is stippled to conform to the auricular lobe of Triturus.

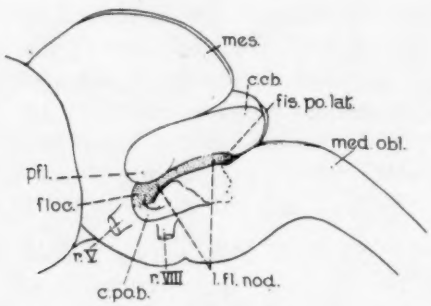


Fig. 3.—Lateral view of the cerebellar region of the opossum pouch young eighteen days after birth (from figure 53, Larsell [7b]).

relations, and that the posterolateral fissure clearly includes the floccular sulcus in embryonic stages. The division into the uvulonodular (postnodular) and the floccular fissure in most adult mammals is due to secondary factors. Contrary to statements frequently made, the posterolateral fissure is the first to appear in the mammalian embryo, as well as phylogenetically. It antedates the fissura prima in both respects, and morphologically it is the most important fissure of the cerebellum.

FLOCCULONODULAR LOBE

The auricular, or flocculonodular, lobe has its origin from the rhombic lip of the medulla oblongata. During development in the mammalian embryo the rostrolateral wall of the recessus lateralis flares outward and becomes thickened above and below the choroid plexus, which closes the recess laterally (figs. 2 to 4 and 7). The thickened upper lip becomes the flocculus. The lower lip becomes the corpus pontobulbare. The corpus pontobulbare is homologous with the acousticolateral area of aquatic forms, with the lateral line tracts and centers omitted (figs. 1 *A* and 3). The upper and lower lips are continuous around the rostrolateral margin of the lateral recess, so that in the earlier stages of

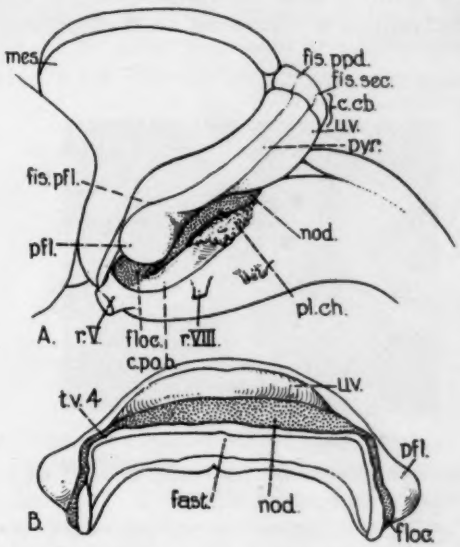


Fig. 4.—Diagrams of the cerebellar region of the opossum pouch young twenty-six days after birth (redrawn from figures 11 and 12, Larsell [7e]). *A* is a dorsolateral view, and *B*, a ventral view.

development of the mammalian cerebellum there is no boundary between the flocculonodular lobe and the pontobulbar body. For this reason, I was inclined to include part of the latter structure with the flocculonodular lobe. It appears better, however, to define the flocculonodular lobe in terms of adult structure, thus excluding all the corpus pontobulbare, which in the adult belongs to the medulla oblongata and not to the cerebellum, although it is continuous with the floccular cortex in many mammals by a thin zone of gray substance. The lobus flocculonodularis thus defined includes the two flocculi, the nodulus and their peduncles (figs. 2 to 5, 7, 8 and 13). The lateral commissure is also included. In some mammals, such as the opossum, there is a continuous

band of cerebellar cortex between the flocculi and the nodulus. In others, as in the adult bat, there is only the fibrous connection of the commissure. This condition has obscured the relationships between the nodulus and the flocculus. In the human brain there are sometimes observed areas of cortex along the peduncles between the flocculi and the nodulus.

CORPUS CEREBELLI

The corpus cerebelli includes all the cerebellum which lies above or rostral to the posterolateral fissure and between its laterorostral extensions (figs. 1 *A* to 8). In reptiles the corpus cerebelli begins to show fissures which may be regarded as representing the boundaries between primitive gyri, or folds of cerebellar cortex. These primitive gyri expand into various subdivisions of the corpus cerebelli, which

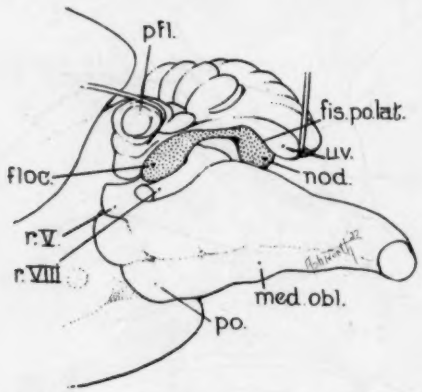


Fig. 5.—Ventrolateral view of the cerebellum and the adjacent region of the adult opossum (redrawn from figure 17, Larsell [7c]). The caudal part of the lateral lobe of the cerebellum has been dissected away to expose the paraflocculus peduncle to the pyramis and uvula, and the paraflocculus has been pulled forward to expose the flocculus and its connection with the nodulus. The nodulus has been exposed by pulling the cerebellum upward from the medulla oblongata.

are further described later in this article. The main fissures appear in the mammalian embryo in the order of their phylogenetic appearance.

Fissures of the Corpus Cerebelli.—Fissura Prima: The fissura prima of Elliot Smith (sulcus primarius of Kuithan) is the first fissure of the corpus cerebelli (fig. 6). Ingvar [10] called attention to a "sulcus anterior" in the cerebellum of Chelonia midas and described a fissure *x* in the alligator and in the chick embryo. I have pointed out elsewhere that the fissure *x* must be regarded as homologous with the fissura prima of mammals. In embryos of the opossum, bat, mole and rat, it is con-

10. Ingvar, Sven: Zur Phylo- und Ontogenese des Kleinhirns, Folia neurobiol. **11**:205, 1918.

siderably later than the posterolateral fissure in making its appearance. In the larger mammals and in man it is somewhat precocious, apparently owing to the large development of the corpus cerebelli in these species. It is preceded by the posterolateral fissure in these embryos also. The name, however, is so embedded in the literature that it should remain.

The fissura prima subdivides the corpus cerebelli into an anterior and a posterior lobe (figs. 6 and 8 to 13). As the surface of these lobes increases with the growth of the cerebellar cortex in the larger reptiles and, especially, in mammals, other fissures appear in each lobe, marking off secondary and tertiary divisions. Continuation of this process results in the familiar gyri of the adult mammalian cerebellum.

Fissura Secunda (figs. 4 and 6 to 13): The fissura secunda of Elliot Smith separates the uvula from the rest of the posterior lobe of the corpus cerebelli early in the development of the mammalian embryo. It is recognizable in the crocodilians and corresponds to Ingvar's fissure

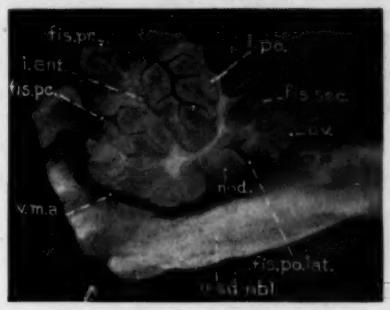


Fig. 6.—Photograph of the cerebellum and medulla oblongata of the adult opossum cut through the sagittal plane (from figure 10, Larsell [7e]).

y of reptiles and birds. It does not extend the full width of the mammalian corpus cerebelli but ends in the peduncles of the paraflocculus. This part of the mammalian cerebellum is developed as a lateral growth of the uvula and the pyramis, the two fusing to form the paraflocculus, around the end of the fissura secunda. The crowding incident to formation of the lateral cerebellar lobes in higher mammals, together with the formation of an elongated peduncle for the paraflocculus, greatly obscures the relationships of the fissura secunda and the adjacent parts in the adult. Embryonic stages in primitive mammals show the relations clearly. The figures of Streeter and others indicate that the same developmental story is true in the human embryo, although the details are lacking since as closely graded stages have not been studied as in lower forms.

Fissura Parafloccularis (figs. 4, 7, 8 and 13): The fissura parafloccularis of Bolk appears in embryos of the bat, opossum, mole and rat

on the lateral surface of the posterior lobe of the corpus cerebelli, a short time after the fissura secunda is recognizable. It marks off the paraflocculus rostrally from the lobulus ansiformis, so that the paraflocculus is developed between this fissure and the lateral part of the fissura posterolateralis.

Fissura Praepyramidalis (figs. 4 and 7 to 13): This fissure may be seen in the embryo a little later than the parafloccular fissure, with which it becomes continuous in the opossum, the bat and some other mammals. It does not do so in the rat and many other forms. It subdivides the lobus medius of Elliot Smith into the pyramis and the lobus medius of Ingvar.

Fissura Praeculminata (figs. 6 and 9 to 13): In the meantime this fissure has begun as a furrow in the anterior lobe of the corpus cerebelli.

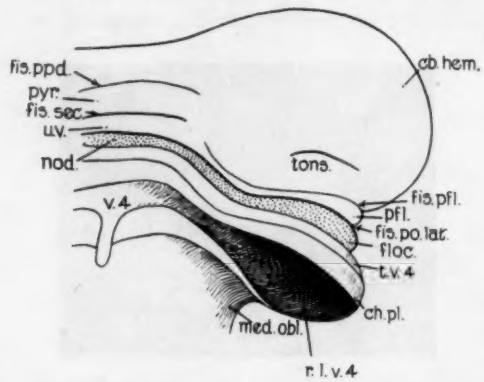


Fig. 7.—Cerebellum of a human fetus of 12 cm. (modified from figure 68, Ingvar [10]).

It appears shortly after the fissura secunda and before the fissura praepyramidalis in all the embryos studied. This is also true phylogenetically. In the marsupial mole, according to Elliot Smith,[11] there is a fissura secunda, but neither the preculminate nor the prepyramidal fissure is observed in the adult of this primitive mammal.

The posterolateral fissure and the five fissures of the corpus cerebelli just described appear to represent the most important boundaries of the cerebellum from the morphologic point of view. Some of these fissures become obscured in the larger mammals and man by the subsequent development of various subdivisions of the cerebellum, but they are the most constant embryologically and phylogenetically.

Subdivisions of the Corpus Cerebelli.—Anterior Lobe of the Corpus Cerebelli (figs. 6 and 8 to 13): This lobe corresponds to the anterior

11. Smith, G. Elliot, cited by Hausman.[42]

lobe of Elliot Smith,[12] Bolk,[13] Ingvar,[10] Riley [14] and, more recently, Abbie.[15] It should be stated that the commissura cerebelli appears to be more closely related to the anterior lobe than to other parts of the corpus cerebelli. Otherwise, I have little to add to previous descriptions of this lobe and its subdivisions.

The anterior lobe shows relatively little lateral expansion, as compared with the posterior lobe, in any of the mammals. Bolk stated that it is not divided into a vermian portion and lateral expansions, as are other parts of the cerebellum. Riley, however, modified this conception and the schema which embodies it so as to give the anterior lobe a hemispheral portion also. The illuminating diagrams of the cerebellum of a large number of mammals in Riley's account substantiate this interpretation. They also suggest that, in general, the mammals which have

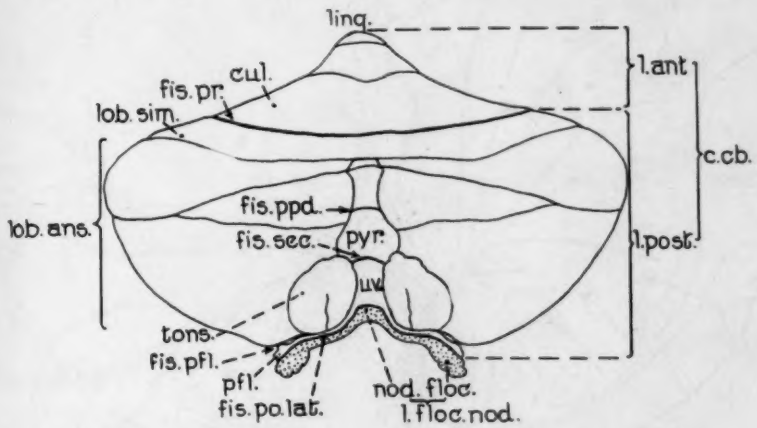


Fig. 8.—Schematic diagram of the adult human cerebellum (modified from figure 73 [5], Ingvar [10]).

the largest development of the muscles of the head and snout have a relatively larger anterior lobe. The closer relation of the commissura cerebelli, with its trigeminal component, to the anterior lobe, as compared with the posterior lobe, and the importance of the trigeminal nerve in the feeding reflexes throughout the vertebrate series, together with

12. Smith, G. Elliot: The Primary Subdivisions of the Mammalian Cerebellum, J. Anat. & Physiol. **36**:381, 1902; Further Observations on the Natural Mode of Subdivision of the Mammalian Cerebellum, Anat. Anz. **23**:368, 1903.

13. Bolk, L.: Das Cerebellum der Säugetiere, Jena, G. Fischer, 1906.

14. Riley, H. A.: The Mammalian Cerebellum: A Comparative Study of the Arbor Vitae and Folial Pattern, A. Research Nerv. & Ment. Dis., Proc. **6**:37, 1929.

15. Abbie, A. A.: The Brain-Stem and Cerebellum of Echidna Aculeata, Phil. Tr. Roy. Soc., London, s.B **224**:1, 1934.

the distribution of the ventral spinocerebellar tract almost exclusively within it, indicate that the anterior lobe represents the most primitive part of the corpus cerebelli.

Posterior Lobe of the Corpus Cerebelli (figs. 6 and 8 to 13): The posterior lobe is bounded rostrally by the fissura prima and caudally and laterally by the posterolateral fissure. It includes the uvula, the pyramis, the paraflocculus, the medial lobe of Ingvar and the lateral extensions of these subdivisions. As I have stated elsewhere, it differs from the posterior lobe of Bolk and of Riley in lacking the nodulus and the flocculi, with their peduncles and connections.

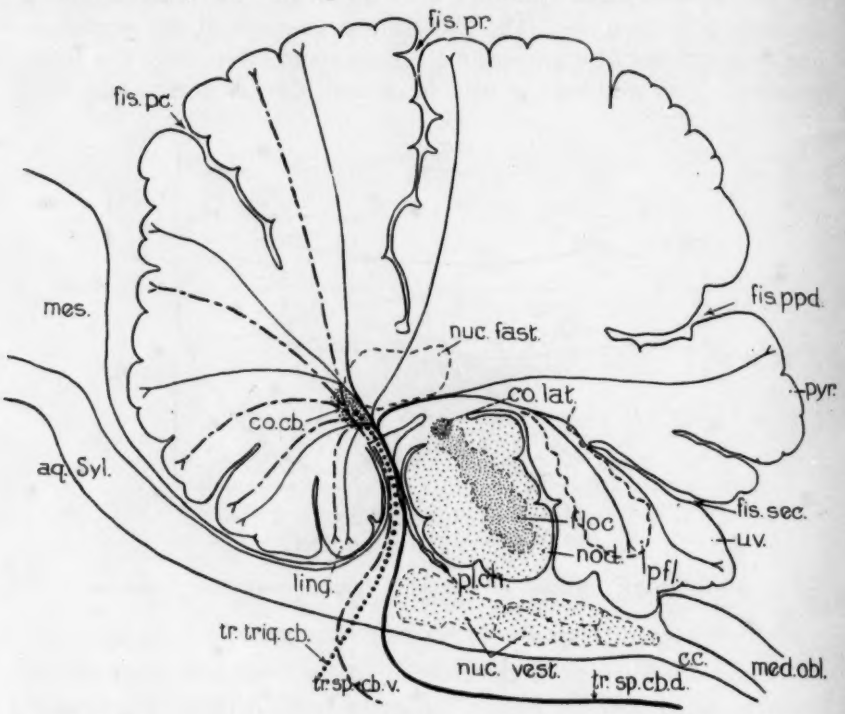


Fig. 9.—Diagram of the trigeminal and spinal connections with the cerebellum in mammals, as shown by Marchi experiments on spinal tracts by various authors cited in the text and by series of Weigert and silver preparations for trigeminal connections. This diagram and those in figures 10, 11 and 12 were drawn in outline from sagittal sections of the cerebellum of a kitten 1 day old, with all but the most important fissures and sulci shown only as slight indentations. This figure and figures 10 and 11 represent projections on the midsagittal plane; figure 12 represents a more lateral plane.

The lateral expansion of the middle or vermian part of the cerebellum to form the lateral cerebellar lobes is most pronounced in the part of the posterior lobe, as here defined, which lies between the fissura

prima and the fissura secunda, i. e., the medial lobe of Elliot Smith. It is associated with great development of various groups of muscles related to the trunk in origin or function. The functional localization of these groups of muscles in relation to the cerebellum will not be attempted at present, save in the most general way. In a description of the cerebellum of snakes and lizards,[16] I pointed out a lateral enlargement in Gerrhonotus which I designated as the pars lateralis, to distinguish it from the tonguelike pars interposita of this lizard. The pars

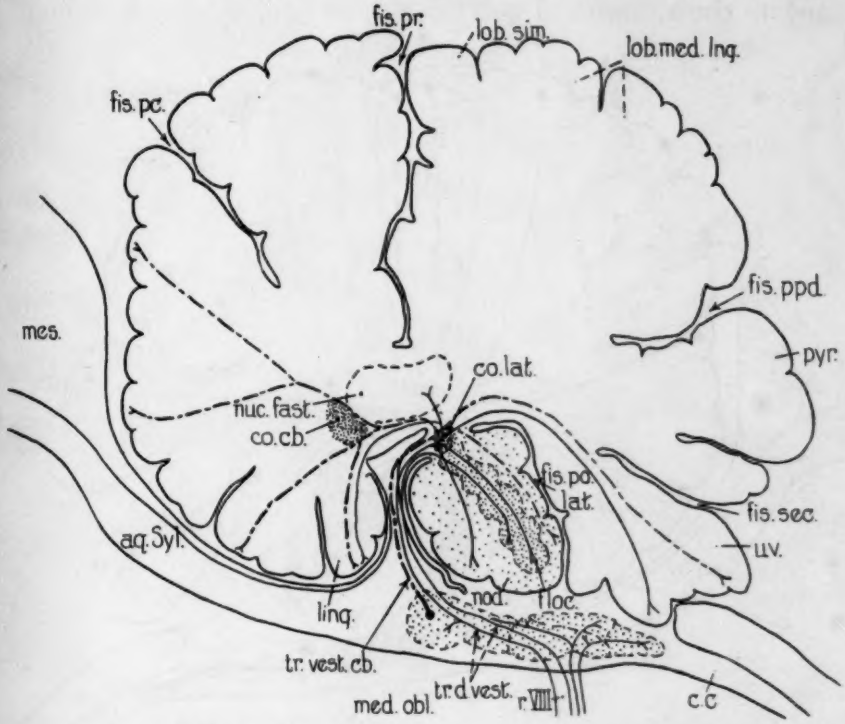


Fig. 10.—Diagram of the chief vestibular connections with the cerebellum, based chiefly on the work of Ingvar and of Dow.

interposita resembles the entire cerebellum of the snake. Gerrhonotus combines a snakelike use of the trunk in locomotion with the use of its rather small legs. The suggestion was made, therefore, that the pars lateralis represents the lobulus ansiformis of Bolk. This part of the mammalian cerebellum is regarded by Bolk, van Rijnberk and others as having to do with the paired appendages. To the comparative evidence

16. Larsell, O.: The Cerebellum of Reptiles: Lizards and Snake, J. Comp. Neurol. **41**:59, 1926.

previously presented I can now add that of the simple cerebellum of the bats Myotis [7] and Corynorhinus,[17] in which the lobulus ansiformis forms the greater part of the lateral lobe of the cerebellum but in which the vermian part of the posterior lobe of the corpus cerebelli is still predominant. There is a shallow furrow, the sulcus paramedianus, between the lateral cerebellar lobe and the medial, or vermian, part of the posterior lobe. In Myotis the ansiform lobule is round and smooth, but in the somewhat larger Corynorhinus there is a small transverse furrow, the sulcus intercruralis, dividing the lobule into the crus primum and the crus secundum of Bolk.

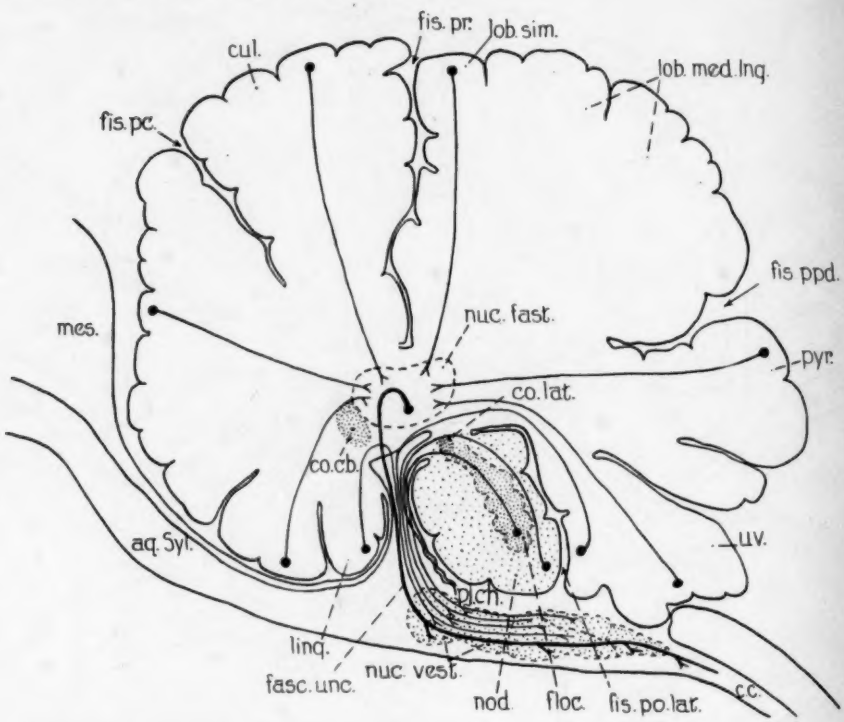


Fig. 11.—Diagram of the connections of the cerebellar cortex with the fastigial and vestibular nuclei.

The attachments and direction of action of the appendicular muscles of these two bats indicate that both the arm and the leg muscles take part in the relatively uncomplicated flapping movements of flying. The slightly larger size of the rudimentary ansiform lobule in Corynorhinus and the appearance of the intercrural sulcus seem to be correlated with

17. Larsell, O., and Dow, R. S.: The Development of the Cerebellum in the Bat (Corynorhinus sp.) and Certain Other Mammals, J. Comp. Neurol. **62**:443, 1935.

the slight increase in the muscle mass of the paired appendages in this species, as compared with Myotis, in accordance with the law of Baillarger. It should be emphasized that the increase in the efferent elements of the cerebellar cortex thus shown represents, primarily, an augmentation of the projection area for proprioceptive impulses from the muscles, tendons and joints involved. The ventral spinocerebellar tract terminates quite medially, but the dorsal tract of Flechsig ends more laterally, according to Beck.[18] The dorsal tract of Flechsig is small in reptiles and large in mammals. In mammals the ansiform lobule is also further increased by the corticopontile-cerebellar connections.

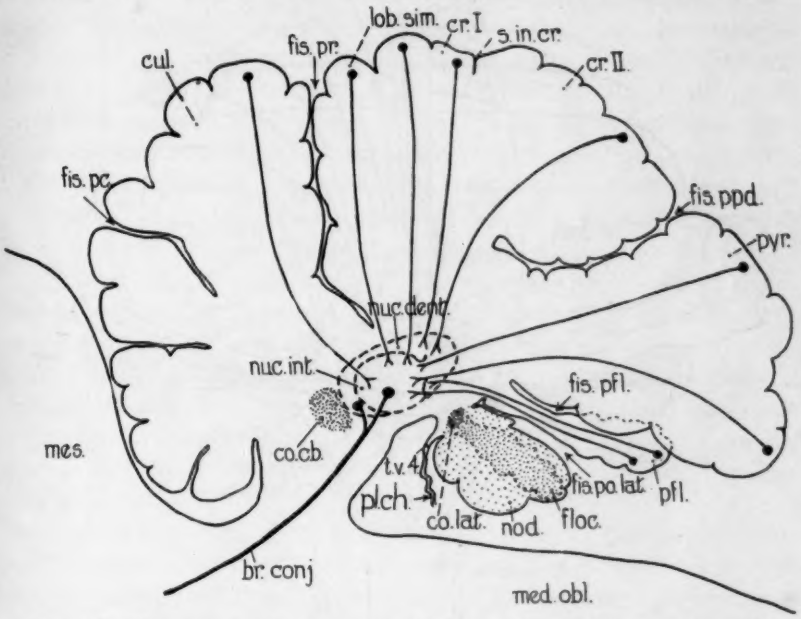


Fig. 12.—Diagram showing the connections of the cerebellar cortex with the nucleus interpositus and the nucleus dentatus.

The cerebellum of turtles and crocodilians appears to be capable of the same interpretation. In turtles the paired appendages represent the most important muscle masses, although the neck muscles must not be ignored. The corpus cerebelli of the turtle does not show lateral lobules, marked off from a median part by sulci, but it is massive laterally and rostrally and is reduced caudally. The massive lateral region is interpreted as foreshadowing the lateral lobes of mammals. In the alligator there are a caudal elongation of the medial part and a lateral swelling of the corpus cerebelli, above the auricles.

18. Beck, G. M.: The Cerebellar Terminations of the Spino-Cerebellar Fibers of the Lower Lumbar and Sacral Segments of the Cat, Brain **50**:60, 1927.

Comparing the cerebellum of Gerrhonotus and the alligator, on the one hand, with that of the small bats, on the other, it is evident that if the cerebellum of the bat were straightened rostrocaudally so as to do away with the curvature and the crowding due to its position, the general pattern would be much the same in these reptiles as in the bats. The pars lateralis of Gerrhonotus and the alligator, although much smaller, corresponds in general to the ansiform lobule of the bats. The pars

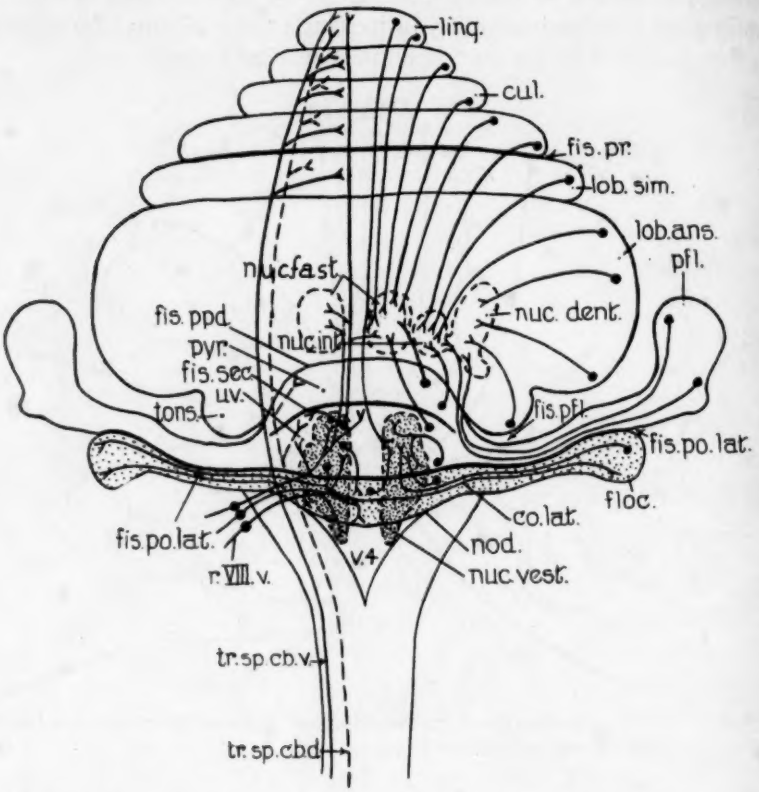


Fig. 13.—Diagram of the mammalian cerebellum and its chief connections. The pontile, olivary and other bulbar connections are omitted.

interposita of the reptiles corresponds to the vermian part of the cerebellum of the bat, with the caudal end of the pars interposita representing roughly the uvula and adjacent parts in the bat. There is nothing in the reptilian cerebellum to suggest the pyramis and the paraflocculus.

Lobus Medius of Elliot Smith: The lobus medius, lying between the fissura prima and the fissura secunda (figs. 6 and 8 to 13), is present in crocodilians and primitive mammals. It, however, with the uvula, comprises a subdivision of the corpus cerebelli which is secondary to

the anterior and posterior lobes already described. It is part of the posterior lobe of the corpus cerebelli. It becomes subdivided, in turn, by the prepyramidal fissure into the pyramis and the lobus medius of Ingvar (figs. 8 to 13). The latter is later in development than Elliot Smith's medial lobe, both phylogenetically and in the embryos of all mammals which possess it. The marsupial mole (Notoryctes) has no fissure corresponding to the fissura praepyramidalis and therefore has no medial lobe of Ingvar, according to the figures of Elliot Smith.

Uvula (figs. 2 and 4 to 13): The uvula must be regarded as a primitive part of the posterior lobe of the corpus cerebelli. It receives both direct vestibular and spinocerebellar fibers, according to Ingvar. It lies nearest the basis cerebelli and the flocculonodular lobe. Functionally, it should be the most generalized part of the posterior lobe, if there are degrees of functional specialization in the cerebellum; i. e., if the primitive corpus cerebelli may be regarded as correlating muscle sense and vestibular impulses, this function would appear to be retained by the uvula. Other parts of the corpus cerebelli have received newer and, presumably, more specialized connections, chiefly secondary, such as fibers from the olive and the pons.

Pyramis (figs. 4 and 7 to 13): The pyramis receives dorsal spinocerebellar fibers but no direct vestibular fibers, according to Ingvar's experimental results with the Marchi method. The dorsal spinocerebellar tract is more recent phylogenetically than the ventral tract of Gowers, which is distributed chiefly to the anterior lobe. This fact may hold some suggestion as to the functional significance of the pyramis. Both the pyramis and the uvula have peduncular connections laterally with the paraflocculus.

Paraflocculus (figs. 3 to 5, 7, 8, 12 and 13): The paraflocculus clearly belongs to the corpus cerebelli and is distinct, phylogenetically and ontogenetically, from the flocculus. Dow [19] has presented experimental evidence that it is distinct also in its fiber connections. It therefore should not be included with the flocculus, either in the formatio vermicularis of Bolk or in the floccular lobe of Elliot Smith. In a previous paper [4] I defined the floccular lobe so as to correspond more accurately with the auricular lobe of lower forms and to exclude the paraflocculus. Because the term, as introduced by Elliot Smith to include the flocculus and paraflocculus in mammals, had been in use for many years, I later substituted the term flocculonodular lobe, as already defined. It appears desirable to abandon the term floccular lobe altogether, since Elliot Smith's use of the term is morphologically incorrect and my use of it in a different sense would lead to confusion. I therefore made the

19. Dow, R. S.: The Fiber Connections of the Posterior Parts of the Cerebellum in the Rat and Cat, J. Comp. Neurol. **63**:527, 1936.

change, in connection with the description of cerebellar development in the bat, and I take this means of adding emphasis to the need of such a change. In the higher primates the paraflocculus becomes greatly reduced. In man it is merely a nodule which appears to be associated with the flocculus. Its embryonic development in man shows its relation to the corpus cerebelli, as in lower mammals, and the time of its appearance is much later than that of the flocculus. There has been much confusion as to its morphologic relations, which detailed study of the developing cerebellum in several mammals has clarified. The adult relations of the flocculus, as described by Riley in many mammals and by Johnston [20] in man, appear to have their explanation in the separate embryonic origins of the flocculus and the paraflocculus.

The paraflocculus has usually been regarded as associated with the flocculus. Its connections, both afferent, so far as they are known, and efferent, as shown by Dow,[19] do not substantiate this conception. Abbie has suggested that trigeminal connections are important in the paraflocculus. Bolk observed that it is well developed in certain mammals, including the whale, which must perform balancing movements to a greater degree than many other mammals. It is relatively large in the bat. Pending more detailed studies, now in progress, on the correlation of muscle masses with the cerebellar pattern in various mammals, further attempts to compare the interpretations of Bolk with the general pattern of the cerebellum suggested here will be held in abeyance. Bolk's interpretations have received considerable experimental support, especially from the studies of van Rijnberk.[21] In connection with the paraflocculus, which Ingvar has shown to receive spinocerebellar but no direct vestibular fibers and which Jansen [22] has proved to be connected with the purely vestibular flocculus by arcuate fibers, the tentative suggestion may be hazarded that it has to do with proprioceptive stimuli, other than vestibular, which play a part in maintaining equilibrium.

Lobus Medius of Ingvar (figs. 8 to 13): This is the most recent phylogenetically of the major subdivisions of the posterior lobe of the corpus cerebelli. Its afferent connections are chiefly with the pons and, through the pons, with the cerebral cortex. The lateral cerebellar lobes are outgrowths of the middle portion of the cerebellum, chiefly of the medial lobe of Ingvar. They become increasingly important with the development of the corticopontile-cerebellar pathways.

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20. Johnston, T. B.: A Note on the Peduncle of the Flocculus and the Posterior Medullary Velum, J. Anat. **68**:471, 1934.

21. van Rijnberk, G.: Die neueren Beiträge zur Anatomie und Physiologie des Kleinhirns der Säuger, Folia neuro-biol. **1**:46, 1908; Weitere Beiträge zum Lokalisationsproblem im Kleinhirn, ibid. **6**:143, 1912.

22. Jansen, J.: Experimental Studies on the Intrinsic Fibers of the Cerebellum: I. The Arcuate Fibers, J. Comp. Neurol. **57**:369, 1933.

It will add to the clarity of the functional and developmental significance if the lobus medius of Ingvar is designated as the neocerebellar part of the posterior lobe of the corpus cerebelli. The pyramis, uvula and paraflocculus may be designated collectively as the paleocerebellar part of the posterior lobe of the corpus cerebelli.

AFFERENT FIBERS

Ventral Spinocerebellar Tract of Gowers (fig. 9).—This tract, which is phylogenetically the oldest, terminates in mammals chiefly in the anterior lobe of the corpus cerebelli, according to the results of McNalty and Horsley,[23] Ingvar[10] and Beck.[18] This is true also in lower vertebrates, such as reptiles, so far as dorsal and ventral tracts can be differentiated. Only one tract is present in Petromyzon, amphibians and many other forms. With trigeminal fibers it forms the commissura cerebelli. McNalty and Horsley observed fibers of the ventral tract reaching the lobulus simplex in mammals, just caudal to the fissura prima, but none to the lingula. Beck described both ventral and dorsal spinocerebellar fibers to the lingula, while Ingvar observed only a few dorsal tract fibers to this part of the anterior lobe.

Dorsal Spinocerebellar Tract (fig. 9).—According to McNalty and Horsley, this tract reaches all parts of the anterior lobe save the lingula and the lobulus simplex, thus overlapping the ventral tract. In addition, according to these investigators, it projects into the posterior lobe of the corpus cerebelli and into the nodulus. Ingvar's results were in agreement, save that he described dorsal tract fibers to the lingula but emphasized the absence of such fibers from the nodulus. He also observed fibers from the dorsal tract to the paraflocculus (page 400). Beck indicated dorsal tract fibers to both the anterior and the posterior lobe and to parts of the medial lobe of Ingvar not included by either McNalty and Horsley or Ingvar.

In one of his diagrams (fig. 24) Beck showed dorsal spinocerebellar fibers to the lateral part of the nodulus. I have found no statement in his text or indication of degeneration in the nodulus in his excellent photographs to substantiate the diagram in this respect. He stated (page 64) that a few degenerated fibers were seen in the stalk of the flocculus, which he was inclined to ascribe to Flechsig's tract. In Beck's experiments, the more medial parts of the nodulus (fig. 25) showed no spinocerebellar fibers, either dorsal or ventral. Save for the wider distribution of the fibers in the lobus medius of Ingvar, Beck's results were in general agreement with those of Ingvar. He added the observa-

23. McNalty, A. S., and Horsley, V.: On the Cervical Spino-Bulbar and Spino-Cerebellar Tracts and on the Question of Topographical Representation in the Cerebellum, Brain **32**:237, 1909.

tion that the dorsal tract of Flechsig is distributed in the lateral part of the vermis, in contrast to the ventral tract, the distribution of which is more caudal. The ventral tract decussates in the cerebellar commissure, while the dorsal tract ends uncrossed.

Intermediate Spinocerebellar Tract.—This tract, described by Pellizzi,[24] was given more detailed attention by Beck. It enters the cerebellum in closer relation to Flechsig's tract than to that of Gowers. It undoubtedly has been considered a part of Flechsig's tract by most investigators of the cerebellum. It is of interest in the present connection in suggesting how the dorsal spinocerebellar tract was formed.

Comparative studies, as already noted, show a single spinocerebellar tract in amphibians, which have no posterior lobe of the corpus cerebelli. There is a small dorsal spinocerebellar tract in the alligator, which has a relatively small posterior lobe. It is not easy to distinguish the dorsal and the ventral tract in reptiles, owing to the presence of intermediate fibers. With the formation of the cerebellar peduncles and the larger posterior lobe of mammals, the two main tracts become widely separated in the medulla oblongata. The somewhat scattered fibers of the intermediate tract are described as ending in the vermis. It would seem likely, on phylogenetic grounds, that most of them end in the uvula, which must be regarded as an ancient part of the corpus cerebelli. The region of the primitive cerebellum which it represents must have received spinal fibers before the tract of Flechsig was differentiated. This tract, however, has not differentiated de novo but has passed through the process outlined, with the small intermediate tract as the connecting link with the primitive condition.

Vestibular Tracts (fig. 10).—The experimental evidence as to the termination of direct and secondary vestibular fibers within the cerebellum is confusing. Ingvar,[10] Winkler,[25] van Gehuchten [26] and others have studied this aspect of cerebellar connections, with various results. The more recent contribution of Dow,[19] based on a study of the cerebellum of rats and cats treated by the Marchi method, showed direct vestibular root fibers to the vestibular nuclei, the fastigial nucleus, the flocculus and the ipsilateral half of the uvula and nodulus. This is in agreement with Ingvar's results. Ingvar observed, in addition, direct

24. Pellizzi, G. B.: Sur les dégénérescences secondaires dans le système nerveux central, à la suite des lésions ou de la section des racines spinales, Arch. ital. de biol. **24**:89, 1895.

25. Winkler, C.: Opera omnia: Le système du nervus octavus, Haarlem, de Erven F. Bohn, 1921, vol. 7, p. 101.

26. van Gehuchten, P.: Recherches expérimentales sur les terminaisons du nerf vestibulaire et sur les voies vestibulaires centrales, Rev. d'oto-neuro-opht. **5**:777, 1927.

vestibular fibers to the lingula. Secondary vestibular fibers, according to Dow, reach both fastigial nuclei, the cortex of both flocculi, the nodulus and the uvula and probably the basilar parts of the anterior lobe.

Trigeminocerebellar Fibers (fig. 9).—The distribution of trigeminal fibers in the cerebellum is little known. It is now recognized that a trigeminal component of the commissura cerebelli exists, as in lower vertebrates. In the opossum there is a fairly distinct nucleus of the cerebellar commissure, corresponding to a cell group described by me in reptiles. In the bat this group of cells is not separated from the superior nuclear mass of the fifth nerve. To what extent the trigeminal fibers of the commissure are distributed to the cerebellar cortex is not known. Presumably, they accompany the fibers of the ventral spinocerebellar tract, with which they are closely associated from a very early stage in the development of the commissure. They would, in that case, be distributed in the anterior lobe of the corpus cerebelli. Abbie, on the basis of the relative size of the trigeminal nerve and the paraflocculus in several mammals, asserted that the paraflocculus has important trigeminal connections. In the bat, with its important trigeminal nerve, large paraflocculus and relatively compact fiber bundles, I have been unable to substantiate this view. Phylogenetically it appears unlikely, in view of the relatively recent development of the paraflocculus and the very early importance of the trigeminal commissure.

Mesencephalic Root of the Fifth Nerve (fig. 1 *A* and B).—The fibers of this root also appear to be related to the cerebellum. They are distinct from those of the trigeminal commissure, not only in their course and termination but histologically. They have an intimate relation to the basis cerebelli both in lower vertebrates and in lower mammals. In Amblystoma, collaterals from the mesencephalic root of the fifth nerve pass to the region of the superior nucleus of that nerve, especially to the part which gives rise to the trigeminal commissure (fig. 1 *A*). Allen [27] observed similar collaterals to the locus caeruleus in the guinea-pig. There is suggestive evidence; but no proof as yet, that the locus caeruleus corresponds to the nucleus of the cerebellar commissure.

In many lower mammals the mesencephalic root of the fifth nerve has an intimate relation to the basis cerebelli. In the opossum such fibers extend through the anterior medullary velum into the base of the cerebellum, and mesencephalic cells of the fifth nerve are observed in the region of the fastigium. Similar observations have been made in the frog.[28] It seems likely that the trigeminal commissure and the

27. Allen, W. F.: Application of the Marchi Method to the Study of the Radix Mesencephalica Trigemini in the Guinea-Pig, J. Comp. Neurol. **30**:169, 1919.

28. Larsell, O.: The Cerebellum of the Frog, J. Comp. Neurol. **36**:89, 1923.

mesencephalic root of the fifth nerve differ functionally but that each plays a part in the foundation of the cerebellum. To what extent they are important in the higher mammals is unknown.

Olivocerebellar Tract.—There has been much confusion regarding the connections of the inferior olive with the cerebellum. Keller,[29] in Marchi material from the cat, traced olivocerebellar fibers only to the posterior part of the "superior vermis." He was unable to follow any such fibers into the lateral lobes. Probst [30] concluded that olivocerebellar fibers reach the anterior and posterior portions of the "superior vermis." Lewandowsky,[31] on the other hand, stated that they reach chiefly the lateral lobes and the flocculus. Holmes and Stewart [32] concluded that they reach all parts of the contralateral cerebellar cortex except the flocculus. Brouwer and Coenen [33] and others differentiated a neocerebellar portion and an older part of the olivocerebellar complex, and Ariëns Kappers [34] asserted that the oldest parts of the inferior olive are connected with the vermis, while the main olivary nucleus is connected with the cortex of the lateral hemispheres.

There is not sufficient detailed information to determine how this system fits into the plan of cerebellar structure outlined in the present review. Shanklin [35] (page 24) was unable to follow fibers from the inferior olive into the cerebellum in the chameleon, which has a well developed olivary nucleus. A small olivocerebellar tract is present in the bat.[7d] Its cerebellar terminations are not known, but it has its origin from a nuclear mass which appears to correspond to the primitive parts of the inferior olive. In the bat, with its relatively small and primitive ansiform lobule, the fibers of this tract, in addition to those which end in the vermis, cannot extend far from the vermian structure. The more specific statement of Holmes and Stewart with regard to fibers from the older parts of the olive, namely, that they reach the vermis and a small part of the hemispheres in man, agrees with this conception of a medial termination. The observations of Keller and of Probst, pre-

29. Keller, R.: Ueber der Folgen von Verletzungen in der Gegend der unteren Olive bei der Katze, Arch. f. Anat. u. Entwcklngsgesch., 1901, p. 177.

30. Probst, M.: Zur Anatomie und Physiologie des Kleinhirns, Arch. f. Psychiat. **35**:692, 1902.

31. Lewandowsky, M., cited by Ariëns Kappers, Huber and Crosby.[1]

32. Holmes, G., and Stewart, T. G.: On the Connection of the Inferior Olives with the Cerebellum in Man, Brain **31**:125, 1908.

33. Brouwer, B., and Coenen, L.: Untersuchung über das Kleinhirn, Psychiat. en neurol. bl. **25**:201, 1921.

34. Ariëns Kappers, C. U.: The Phylogenetic Development of the Cerebellum, Psychiat. en neurol. bl. **38**:788, 1934.

35. Shanklin, W. M.: The Central Nervous System of Chameleon Vulgaris, Acta zool. **11**:425, 1930.

viously cited, are suggestive, if "superior vermis" can be interpreted to mean the pyramis, the culmen and possibly the lobulus simplex, which receive spinocerebellar but no direct vestibular fibers. Certainly, the nodulus, uvula and lingula can be omitted from the areas of termination.

Arcuate-Cerebellar Systems.—These paths are the basis of much lack of agreement as to their connections with and relations to the cerebellum. Reference may be made to Ariëns Kappers, Huber and Crosby [1] (page 803) for a review of the literature. The fibers seem to be superimposed on older structures and not to affect the main pattern presented here.

Reticulocerebellar Fibers.—These tracts and others have also been described but need not be included in the present discussion.

Tectocerebellar Tract.—This tract occurs in lower vertebrates and in primitive mammals. That it has not been demonstrated in higher mammals is not sufficient reason to assume that it does not exist. In aquatic forms there is also a mamillocerebellar tract, which apparently disappears with the assumption of the land habitat. Both tracts connect with the primitive anterior lobe, but the manner and specific location of their terminations are not known. The mamillocerebellar connections must be regarded as performing for the gustatory and olfactory centers in aquatic forms the same type of function that the tectocerebellar connections perform for optic and auditory centers in land animals.

Corticopontile-Cerebellar Tracts.—These tracts need only be mentioned as the most recent afferent group added to the organ. They constitute relatively small bundles in the bat and larger structures in the opossum. They terminate chiefly in the lateral expansions of Ingvar's medial lobe. Abbie [15] asserted that corticopontile fibers from the frontal lobe of the cerebrum end chiefly in the pretrigeminal part of the pons, whence their impulses are relayed to the region of the declive and tuber of the posterior lobe. The temporopontile fibers, on the other hand, terminate chiefly in the retrotrigeminal portion of the pons, with relays to the culmen of the anterior lobe. This interpretation is suggestive and should be examined by experimental methods. If correct, it does not appear to me that it would modify the fundamental plan of cerebellar structure and development presented in this paper. It would merely superimpose a cortical connection within the anterior and posterior lobes of the corpus cerebelli on the more primitive connections already present.

Summary of Cerebellar Connections.—The cerebellum must be regarded as a complex suprasegmental structure, comparable with the cerebrum. It receives in mammals five principal groups of fibers, namely: (1) direct and secondary vestibular fibers, which pass primarily into the

flocculonodular lobe, but secondarily into adjacent parts; (2) trigeminal fibers, including the mesencephalic root of the fifth nerve; (3) spinocerebellar fibers, which pass primarily into the vermian part of the anterior lobe and the uvula and pyramis of the posterior lobe of the corpus cerebelli; (4) olivocerebellar connections, and (5) cerebrocerebellar fibers, including the tectal connections.

The various systems overlap to some extent in their distribution, but the flocculonodular lobe may be regarded as the primary projection area of vestibular fibers and the pyramis and culmen as the primary area for spinocerebellar fibers, while the uvula and lingula represent areas in which vestibular and spinal fibers overlap. The lobulus simplex and the paraflocculus also appear to receive spinal fibers, but they must receive others concerning which there is no certain evidence. The olivary and arcuate connections may play a part here and in the medial lobe of Ingvar, but the evidence is confusing and incomplete.

In addition to the overlapping of afferent fibers in certain areas of the cerebellum, corresponding to that in the association areas of the cerebral cortex, the cerebellar gyri are also connected by arcuate fibers, as shown by Clarke and Horsley [36] and as carefully studied more recently by Bender [37] and Jansen.[22] Such fibers connecting adjacent cerebellar parts occasionally appear to form bundles of sufficient size to obscure portions of separating sulci and fissures. An example of considerable importance is the posterolateral fissure, which is continuous in lower forms and in the early embryos of mammals, as well as in the human embryo. In many mammals and in man it becomes divided into the floccular and the uvulonodular fissure of adult anatomic structure. This may be due to the formation of bands of arcuate fibers between the uvula and the nodulus laterally, which Jansen described in considerable number, although Bender stated that they are few. The cerebellum thus does not differ greatly from the cerebrum in the general plan of organization. As the cerebrum is founded on the olfactory system, the cerebellum is based on the vestibular system. The vestibular system has become overshadowed by the more general proprioceptor system in mammals, just as the olfactory system has become submerged by other features of the cerebrum. The deep nuclei of the cerebellum may also be compared in a general way to the nuclei of the corpus striatum in development and functional relations to their respective cortices.

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36. Clarke, R. H., and Horsley, V.: On the Intrinsic Fibers of the Cerebellum, Its Nuclei and Its Efferent Tracts, Brain **28**:13, 1905.

37. Bender, Lauretta: Corticofugal and Association Fibers Arising from the Cortex of the Vermis of the Cerebellum, Arch. Neurol. & Psychiat. **28**:1 (July) 1932.

CEREBELLAR NUCLEI

The deep nuclei of the cerebellum confirm in their development and connections the structural pattern I have described. The principal features of their phylogenetic development have been reviewed by Ariëns Kappers, Huber and Crosby [1] and by me.[4] Dowd [38] followed in detail their development in the embryo of the pig. His results showed recapitulation of phylogenetic development. Studies of the connections of these nuclei by the Marchi method are illuminating and will be reviewed briefly.

Vestibular Nuclei (fig. 13).—Clarke and Horsley saw indications of fibers from the cerebellar cortex to the vestibular nuclei only after extensive lesions. Sharp localization of the origin of the fibers was impossible in this part of their experiments. They included the "anterior pennate lobe," the anterior parafloccular lobe and the paramedian lobe in one animal and the culmen and all the middle lobe in another, with degenerated fibers extending to the nucleus dentatus, the nucleus interpositus and the nucleus fastigii, as well as to the vestibular nuclei. Allen [39] described a few fibers to the vestibular nuclei from the "vermis" of the guinea-pig and Saito,[40] from both sides of the "vermis" in the rabbit. The more recent studies of Hohman [41] and Dow [19] were in general agreement. Those of Dow were more specific as to the origin of the fibers. He performed his degeneration experiments on cats and rats, confining his attention to the posterior lobe of the corpus cerebelli and the flocculonodular lobe. He observed that the nodulus and flocculus send their efferent fibers chiefly into the vestibular nuclei. The uvula also sends part of its efferent fibers to these nuclei.

Hohman in cats and Saito in rabbits observed fibers also from the anterior "vermis" to the vestibular nuclei. From the phylogenetic point of view, it would be desirable to know more specifically which part of the anterior vermis is involved. If the interpretation herein set forth is correct, efferent fibers from at least part of the anterior vermis to the vestibular nuclei would correspond to those from the uvula. Both these parts are old in phylogenetic development and should show, with the flocculonodular lobe, the most primitive connections, both afferent and efferent. As has already been stated, this is true of the anterior

38. Dowd, L. W.: The Development of the Dentate Nucleus in the Pig, J. Comp. Neurol. **48**:471, 1929.

39. Allen, W. F.: Distribution of the Fibers Originating from Different Basal Cerebellar Nuclei, J. Comp. Neurol. **36**:399, 1924.

40. Saito, M.: Experimentelle Untersuchungen über die inneren Verbindungen der Kleinhirnrinde und deren Beziehungen zu Pons und Medulla oblongata, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **23**:74, 1922.

41. Hohman, L. B.: The Efferent Connections of the Cerebellar Cortex, A. Research Nerv. & Ment. Dis., Proc. **6**:445, 1929.

vermis with respect to its afferent fibers. As shown by Ingvar in Marchi material in the cat and as less certainly confirmed by me in silver preparations in the bat and opossum, the lingula receives direct vestibular and spinocerebellar fibers, thus corresponding with the uvula. The degenerated fibers to the vestibular nuclei observed by Clarke and Horsley from lesions involving the culmen and the middle lobe should probably be attributed to the culmen. If such efferent fibers are present, it would indicate that the older anterior lobe is less differentiated into regions with distinct connections than the newer posterior lobe, since the pyramis does not appear to have direct efferent vestibular connections.

Nucleus Fastigii (figs. 9 to 11 and 13).—There is general agreement among investigators that fibers from various parts of the vermis pass to the fastigial nucleus. Dow agreed with Ingvar that the vermis consists of separate parts, with distinct fiber connections. Here again, the more specific statements of Dow are illuminating. According to his results, fibers from the uvula pass chiefly to the fastigial nucleus, while only some fibers from the nodulus do so. Clarke and Horsley observed fibers from the pyramis to the roof nucleus, and Dow, more specifically from the medial pyramis. There would thus be brought to this nucleus the partly correlated vestibular and muscle sense impulses from the uvular cortex, together with impulses from the vestibular nodulus and the more spinal pyramis.

The fastigial nucleus thus becomes a correlating center primarily for vestibular and spinocerebellar impulses, after the modification to which they are subjected in the cortex of the parts named. This holds, of course, also for the parts of the anterior lobe in which direct vestibular and spinocerebellar fibers terminate. This nucleus, therefore, must be regarded not as largely vestibular, as has been the tendency, but as the chief nucleus for correlation of vestibular and other stimuli, principally those of muscle sense, which reach the cerebellar parts with which it is connected. It is the most primitive of the true cerebellar nuclei, as shown by its afferent connections with the older parts of the corpus cerebelli, namely, the anterior lobe and the uvula and pyramis of the posterior lobe, in addition to its connections with the nodulus of the flocculonodular lobe. Its efferent connections, which for convenience may all be included with the uncinate fasciculus, are also primitive, passing to the vestibular nuclei, the bulb and the spinal cord.

Nucleus Interpositus.—This nucleus receives fibers from the more medial part of the portions of the cerebellar cortex which are not entered by direct vestibular fibers (figs. 12 and 13). Dow and Hohman both named the lobulus simplex, and Dow included the lateral portion of the pyramis and paraflocculus. Hohman's fibers from the anterior vermis

probably included those from the culmen described by Clarke and Horsley. Dow also included crus I of the lobulus ansiformis and, as already stated, the paraflocculus. Clarke and Horsley included the uvula. These divisions are the earliest to differentiate from the corpus cerebelli in mammals.

Nucleus Dentatus.—This, the most recently developed nucleus, receives its fibers from the lobulus ansiformis and its subdivisions and from the paraflocculus (figs. 12 and 13). These relations appear to conform to Ariëns Kappers' law of neurobiotaxis. In reptiles, in which the pars lateralis is just appearing phylogenetically, the lateral nucleus consists of a single mass of cells. In the lower mammals, in which there are a lobulus ansiformis and a paraflocculus, this nucleus has divided into the nucleus interpositus and the nucleus dentatus. The latter increases in size in relation to the development of the ansiform lobule and its secondary lobules. The relative size of the paraflocculus also determines the size of the ventrolateral outgrowth of the dentate nucleus, namely, the pars paraflocculari s. Hohman's summary of the results of Clarke and Horsley, namely, that the efferent fibers from various parts of the cerebellar cortex "are all ipsilateral and go to the nearest underlying nuclear mass," can perhaps be stated in terms of development as due to the neurobiotactic effect on the nuclear masses caused by stimuli from the various areas of the cortex, according to the period and degree of development. The nucleus dentatus is thus the nucleus of the most recently acquired part of the cerebellar cortex, namely, that of Ingvar's medial lobe. The nucleus interpositus and the nucleus dentatus both send their efferent fibers forward into the midbrain to connect with the nucleus ruber. According to Allen [39] and others, part of the brachium conjunctivum also passes to the thalamus. Whether this may be derived from the dentatus alone is not known.

NEOCEREBELLUM AND PALEOCEREBELLUM

The terms paleocerebellum and neocerebellum have a certain value, if it is recognized that there is no real boundary between the regions they designate. As is evident from the preceding description, the lateral parts of the corpus cerebelli in mammals are outgrowths of the medial, or vermian, portion. The pars lateralis of reptiles foreshadows the lateral lobes of the mammalian cerebellum. The anterior lobe of the corpus cerebelli shows the smallest lateral expansion of any major division. This is the oldest part of the corpus cerebelli; yet even here there is some lateral expansion, especially in Bolk's lobulus 4. Hausman [42] stated that a neocerebellar equivalent is provided for each lobule of the vermis

42. Hausman, L.: The Comparative Morphology of the Cerebellar Vermis, the Cerebellar Nuclei and the Vestibular Mass, A. Research Nerv. & Ment. Dis., Proc. **6**:193, 1929.

except the lingula. Yet the oldest part of the cerebellum phylogenetically, namely, the flocculus, which is connected with the newer vermian nodulus by primitive peduncles and by an ancient commissure, is the most laterally placed developmentally of the cerebellar divisions. It is only by the growth above and around it of other parts of the cerebellum that it has become located relatively near the midplane in larger mammals.

The emphasis on the vermis as a functional entity has been misleading. The vermis is made up of distinct units—some closely related to the ancient vestibular foundation of the cerebellum, others with spinal connections and still others with the newer connections established by the higher centers. Only if the primate cerebellum is taken as the model form, in spite of its greatly hypertrophied ansiform lobule, can the vermis be regarded to some degree as a separate division.

The term neocerebellum is useful, if it is applied in a general way to the region which receives pontile fibers predominantly. The term paleocerebellum should be restricted to the more basal region which receives spinal and vestibular fibers chiefly.

It must be recognized that there are several degrees of newness in the phylogenetic formation of the cerebellum. First appeared the lateral commissure between the acousticolateral areas of the medulla oblongata and then the trigeminal commissura cerebelli between the primary proprioceptive centers. Along each of these commissures there occurred a migration of cells, building a massive corpus cerebelli and a less massive flocculonodular lobe. In land animals the proprioceptive corpus cerebelli became predominant. It soon underwent division into an anterior and a posterior lobe, the latter a new development largely in connection with the growth of the dorsal spinocerebellar tract. This in turn was divided by the fissura secunda into the still newer medial lobe of Elliot Smith and the uvula. The uvula is the more primitive part, as shown by its retention of direct vestibular, as well as spinocerebellar, fibers. Elliot Smith's middle lobe was again subdivided into Ingvar's medial lobe and the pyramis, each with lateral expansions. In the larger mammals the lateral expansions, i. e., the cerebellar hemispheres, become so large as to obscure the medial structures from which they have their origin. It is the medial lobe of Ingvar, with its great lateral development and its connections through the pons with the cerebral cortex, which is the newest major division of the cerebellum, both phylogenetically and functionally.

Phylogenetically, there is basis for division into the archicerebellum, the paleocerebellum and the neocerebellum. The boundaries, especially that between the archicerebellum and the paleocerebellum, cannot be sharply fixed, but in general the archicerebellum should include the flocculonodular lobe and the basis cerebelli, with part of the anterior lobe of the corpus cerebelli and possibly part of the posterior lobe.

The deep nuclei of the cerebellum tell the same story. The fastigial nucleus is the oldest developmentally, corresponding to the nucleus cerebelli of lower vertebrates. Its primitive efferent and afferent connections are retained. It is the nucleus of the first story of the cerebellar superstructure, having to do chiefly with vestibular and muscle sense impulses. The vestibular nuclei are the nuclei primarily of the more purely vestibular flocculonodular "basement." The nucleus interpositus, so far as may be judged from comparative anatomy, has to do chiefly with spinocerebellar stimuli, and possibly others, including those brought by olivocerebellar connections. The nucleus dentatus is the nucleus of the third, or neocerebellar story, so far as the term neocerebellum is justified. It is dominated by corticopontocerebellar impulses. The continuation of fibers from this nucleus to the thalamus, pointed out by Allen,[39] is significant. The connections with distinct parts of the cerebellar cortex demonstrated for these nuclei would seem to indicate that they have different functional values. The tentative conclusions from comparative and experimental anatomic studies, however, must be checked by other methods. The suggestions made in this paper will serve a useful purpose if they point the way for physiologic experiments.

The structural plan of the cerebellum outlined here does not rule out a certain amount of localization of function. Rather, with reference to the primitive distribution of afferent fibers especially, it favors such an interpretation, which is also supported by experimental anatomic evidence. It must be recognized, however, that, in mammals at least, there has developed so much overlapping of fibers from various sources that the primitive pattern is entirely hidden. The two fundamental divisions, namely, the corpus cerebelli and the flocculonodular lobe, receive primarily general proprioceptive and vestibular fibers, respectively. The various tracts which enter the corpus cerebelli of mammals, in addition to trigeminal, spinocerebellar and possibly tectocerebellar fibers, appear to do so secondarily. Some of these, however, assume a functional importance which appears to transcend that of some of the more direct connections.

From the functional point of view, there are four principal divisions of the cerebellum. These are: (1) the vestibular flocculonodular lobe, having its chief afferent connections with the vestibular nuclei; (2) the vestibular and spinocerebellar anterior lobe, the uvula and, in part, the pyramis (spinocerebellar portion), having efferent connections chiefly with the fastigial nucleus and, through the uncinate bundle of Russell, with the vestibular nuclei, the medulla oblongata and the spinal cord; (3) the lobulus simplex, the pyramis in part, the paraflocculus and the lobulus ansoparamedianus, connecting with the nucleus interpositus and through it with the nucleus ruber and, possibly, the thalamus, and (4) the medial lobe of Ingvar, connecting with the nucleus dentatus and through it chiefly with the nucleus ruber and the thalamus.

Obituaries

WILLIAM ALANSON WHITE, M.D.

1870-1937

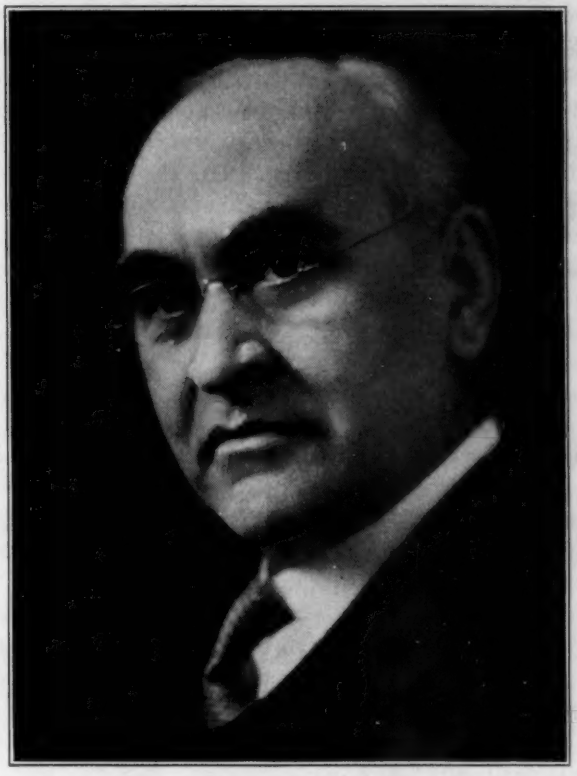
Dr. William Alanson White, psychiatrist, teacher, author and administrator, died of acute sigmoid diverticulitis on March 7, 1937, at his apartment in St. Elizabeths Hospital, Washington, D. C. He was born Jan. 24, 1870, in Brooklyn Heights, N. Y., of old New England stock, the son of Alanson White and Harriet Augusta Hawley. After attending the public schools of Brooklyn, he won a scholarship in Cornell University, where he selected courses in the natural sciences and became clearly oriented in biologic thought. His medical training was taken at the Long Island Medical College, where he received the degree in 1891. He then served as ambulance surgeon and house surgeon, Alms and Work House Hospital, Blackwell's Island, N. Y., and as house physician and surgeon, Long Island College Hospital, Brooklyn. In 1892 he joined the staff of the Binghamton (N. Y.) State Hospital, where he served for eleven years, resigning as first assistant physician in 1903 to become superintendent of St. Elizabeths Hospital at the invitation of President Theodore Roosevelt. To St. Elizabeths Hospital he gave the rest of his life, which was signalized throughout by outstanding organizing ability and superior scholarly attainments.

In 1918 Dr. White married Mrs. Lola Thurston, who survives him. She was a devoted, sympathetic companion during his most mature and productive years.

Any biographic sketch that may be prepared must fail to do justice to the significance of Dr. White's personality and accomplishments, for he not only vitalized and developed the unique institution of which he was the head but his personal influence and published works constitute a large part of American psychiatry. During a period of over forty years he labored to improve medical education in general and psychiatric knowledge in particular. An illuminating account of these years of work and devotion to an ideal may be read in his autobiographic work, "Forty Years of Psychiatry" (Nervous and Mental Disease Monograph Series, no. 57, Washington, D. C., Nervous and Mental Disease Publishing Company, 1933), which, in addition to being an autobiography, reveals a broad perspective of contemporary psychiatric thought and practice.

In the early years of his experience at the Binghamton State Hospital, he became acquainted with Dr. Smith Ely Jelliffe, of New York; each found an understanding friend and co-worker. The results of

the community of interests of this team are shown in an exceedingly productive output of neuropsychiatric literature, including "Diseases of the Nervous System, a Text-Book of Neurology and Psychiatry" (now in its sixth edition), the editing of a two volume work by British and American authors, entitled "The Modern Treatment of Nervous and Mental Diseases," numerous special monographs and articles and the translation of foreign works. They also organized the "Nervous



WILLIAM ALANSON WHITE, M.D.
1870-1937

and Mental Disease Monograph Series" and, stimulated by the then recent developments in psychoanalysis, founded the *Psychoanalytic Review* in 1913.

Dr. White was one of the few mature psychiatrists in whom active interests became aroused by the new psychoanalytic doctrines. He saw the great possibilities in the psychoanalytic approach, which might lead not only to a better understanding and more efficient treatment of mental disorders but to a more comprehensive interpretation of all

human behavior. Open-mindedness was an outstanding characteristic, and he was ever eager to study, consider and evaluate new theories and methods relating to human affairs; it may be said, however, that his attitudes and writings were definitely influenced through his later years by the attainments of the psychoanalytic movement.

In 1907 he released the "Outlines of Psychiatry," a useful textbook for students, which has gone through fourteen revised and elaborated editions. His bibliography from 1894 to 1936 is a large one, in which are to be found an unusual number of special monographs and books, including "Mental Hygiene of Childhood, "Foundations of Psychiatry," "Medical Psychology," "Lectures in Psychiatry," "Mental Mechanisms," "Essays in Psychopathology," "The Meaning of Disease," "Insanity and the Criminal Law," "Principles of Mental Hygiene" and "Thoughts of a Psychiatrist on War and After." His publications reveal clearly that he devoted his lifetime to the detailed study of the nature of mental activity. From his central idea that mind is strictly a function concerned in the adaptation of the person to the environment, he developed his various theses along both scientific and philosophic lines.

Dr. White was always interested in the interrelationships of the various branches of science, and particularly in comparing and contrasting the problems of the medical internist, on the one hand, and the psychopathologist, on the other. He emphasized that the former is concerned chiefly with the functions and pathologic reactions of the organs constituting the body, and the latter, with the relationships between the individual person and the world in which he has to maintain an existence at a certain level of adjustment. Dr. White believed that the psychiatrist's principal constructive rôle is in the realms of social pathology, but he also advocated the concept of the psychobiologic "organism as a whole," in which the functioning of the bodily organs and parts is included in the reaction patterns of the organism. He consistently maintained that the behavior patterns of the organism, including pathologic phenomena, can be explained only by a knowledge of their antecedents and that a psychosis constitutes a variety of reaction which can be interpreted only when the complete developmental history of the organism is known, together with the particular goals in life.

Dr. White was by nature a student and philosopher. An omnivorous reader in many branches of science, he had an unusual, in fact a unique, ability to synthesize into a unified concept the thoughts and contributions of others, often on diverse subjects. Moreover, he could with great facility reduce to simple terms and explain in understandable language the principal points in a research contribution that had perhaps been presented by the originator in a more complex and involved way. He never failed to encourage original work in the beginner and never hesitated in a medical or scientific gathering to speak in the

defense of any young essayist who might be receiving an undue amount of criticism. He could detect something worth while in every attempted contribution and did not object to speculation and advanced hypotheses in matters which it was not yet possible to investigate with experimental methods.

That his abilities and accomplishments were recognized by his contemporaries is shown by the many honors he received. He served as president of the American Psychiatric Association, the First International Congress for Mental Hygiene, the American Psychopathological Association, the American Psychoanalytic Association and several more local organizations. He was a member of the Federal Board of Hospitalization, the executive committee of the National Committee for Mental Hygiene, the Washington Academy of Sciences, the American Neurological Association, the American Medical Association, the American College of Physicians, the American Institute of Criminal Law and Criminology and others. Honorary degrees were bestowed on him by Brown University and George Washington University.

As a teacher, he was outstanding in the lecture room and in the presentation of clinical material, the room usually being packed with students and extracurricular auditors. He was appointed professor of psychiatry at George Washington School of Medicine in 1904 and for many years had a similar chair at Georgetown University School of Medicine. He was lecturer on military psychiatry in the United States army and navy medical schools, being the first to have that title. In addition to his formal duties as a teacher, he was in constant demand throughout the United States as a public speaker, particularly on the topics of mental hygiene and forensic medicine, and his oratorical gifts never failed to inspire an audience.

The long list of examples of scholarly production, of original thinking, of professional attainments and of devotion to work that one might associate with William A. White's name and career constitutes but a portion of his distinction. In the minds of his numerous assistants, students and friends, there are more important considerations. They remember him as he was known everywhere—as a kindly and lovable personality; a genial, friendly man; a fair-minded judge of human situations, and a vital stimulating force to those in need of understanding and help.

An inspiring, thought-provoking writer, enriching psychiatric literature more than any other author of his generation; a brilliant orator; a practical idealist; a contributing member of a community in which he lived—his friends and acquaintances sincerely mourn his passing and cherish the memory of those remarkable qualities of character that were enjoyed by all who knew him.

NOLAN D. C. LEWIS, M.D.

Abstracts from Current Literature

Anatomy and Embryology

CHEMICAL ANALYSIS OF OTOLITHS AND ENDOLYMPHATIC SAC DEPOSITS IN AMBLYSTOMA TIGRINUM. A. B. HASTINGS, J. Comp. Neurol. **61**:295 (April) 1935.

Roentgen spectograms of the powdered sac deposits and otoliths showed a rich content of calcium carbonate in the form of aragonite and the presence of a slight amount of calcium phosphate, presumably dahlite (carbonate apatite).

ADDISON, Philadelphia.

LIMB MOVEMENTS STUDIED BY ELECTRICAL STIMULATION OF NERVE ROOTS AND TRUNKS IN AMBLYSTOMA. J. S. NICHOLAS and D. H. BARRON, J. Comp. Neurol. **61**:413 (June) 1935.

This study is an investigation of the form and connections of the normal brachial plexus, the functional changes occurring after transplantation and the variations in response caused by excision of the embryonic limb. Six animals on which limb transplants or extirpations had been performed in the embryonic stage and six normal animals were tested electrically to determine the function and the segmental distribution of three motor nerves of the brachial plexus. Unipolar stimulation of the nerves revealed that: motor roots have no specific functional distribution pattern in the limb and the response of the motor functional pattern in the limb is more consistent through stimulation of dorsal than of ventral roots; removal of the embryonic limb rudiment not only results in subsequent ganglionic hypoplasia but changes the distribution of the fibers within the cord; the sensory roots arising from hypoplastic ganglia produce responses characteristic of segments posterior to the brachial region, and sensory stimulation results in movements which are limited to their segmental motor component. These results demonstrate that the sensory component of the amphibian nervous system is exceedingly important in coordinating the activity of groups of muscles.

ADDISON, Philadelphia.

THE CHANGE IN VOLUME OF THE OLFACTORY AND ACCESSORY OLFACTORY BULBS OF THE ALBINO RAT DURING POSTNATAL LIFE. C. G. SMITH, J. Comp. Neurol. **61**:477 (June) 1935.

Serial sections were prepared of the anterior part of the forebrain with the bulbs attached, and the volume of the bulbs was determined at representative ages in the postnatal life of the rat. The olfactory bulb is divided into four parts: (1) formatio olfactoria, (2) formatio vomeronasalis, (3) pars bulbaris and (4) ependyma and ventricularis bulbi. The first two divisions are primary, independent centers. These, with the portions of the internal fiber tract and the lateral ventricle which lie anterior to the level of the forward-extending tip of the cortex of the lateral olfactory gyrus, were included in the volume determinations. After the age of 1 year the olfactory center showed marked alteration in structure characterized by atrophy of the olfactory nerves and the glomerular and outer fiber layers. The volume of the olfactory center showed a variation amounting to 20 per cent, in rats of the same age and sex. No recognizable alteration in structure was associated with this variation. Some bulbs showed distinct stunting, amounting to a reduction of 30 per cent from the volume of the smallest bulb in the normal range. The volume of the vomeronasal center showed a variation amounting to 35 per cent, in animals of the same age and sex. At birth the volume of the olfactory center was 2.63 cu. mm.; at 21 days, 29.87 cu. mm., and

at 1 year, 46.37 cu. mm. The volume of the vomeronasal center at birth was 0.25 cu. mm.; at 21 days, 1.18 cu. mm., and at 1 year, 1.39 cu. mm. The loss in volume in old age is due to decrease in the bulk of the entering nerve fibers.

ADDISON, Philadelphia.

THE REACTION OF THE COCHLEAR NERVE TO DESTRUCTION OF ITS END ORGANS: A STUDY ON DEAF ALBINO CATS. HOWARD A. HOWE, J. Comp. Neurol. **62**:73 (Aug.) 1935.

In adult deaf albino cats the lesion is restricted practically exclusively to the structures of the cochlear duct, although there is also collapse of the sacculus with concomitant degeneration of hair cells in its macula. There are complete disappearance of all hair cells and a varying amount of damage to their supporting elements. Nerve fibers and cells of the spiral ganglion appear practically normal. Counts of ganglion cells made on eighteen ears varied from 23,854 to 55,052. In normal ears the range was from 44,298 to 57,494. In albinotic kittens the count was as high as in the normal cat, although the hair cells were destroyed. Howe concludes that the cochlea has developed normally, that some unknown agent has caused, first, the disappearance of hair cells and, later, destruction of all the cells in the organ of Corti and that changes in the ganglion cells and nerve fibers have taken place later and are secondary.

ADDISON, Philadelphia.

THE NISSL GRANULES OF AUTONOMIC NEURONES. W. H. HOLLINSHEAD and SAM L. CLARK, J. Comp. Neurol. **62**:155 (Aug.) 1935.

Autonomic ganglia were collected as soon after death as possible from the rat, guinea-pig, cat, dog, sheep and man. Cats were chosen for quantitative studies. Cells with two main patterns of Nissl granules were observed: (1) those with a marked peripheral ring of Nissl granules and a zone more or less free from granules between this ring and the nucleus, and (2) those with the cytoplasm diffusely filled with Nissl granules and no definite condensation at the periphery. More than 30 per cent of cells in all ganglia showed the diffuse Nissl arrangement. The ring type predominates in the ciliary, superior cervical and celiac ganglia. Ciliary ganglia from different animals include approximately the same proportions of the two main types of cells, with an intermediary type. Studies of these ganglia were made from nine to fourteen days after injury to the nerve. Chromatolysis occurred in both types of cells after axonal injury.

ADDISON, Philadelphia.

A COMPARATIVE CYTOARCHITECTONIC STUDY OF THE MOTOR AND PREMOTOR AREAS IN THE PRIMATE CORTEX. PAUL C. BUCY, J. Comp. Neurol. **62**:293 (Oct.) 1935.

The purpose in this study was to observe the anatomic limits of the motor and premotor cortex in a large variety of primates: Lagothrix Humboldtii, Ateles ater, Macaca mulatta, Papio papio, Pongo pygmaeus and Pan satyrus.

Cellophane tracings were made of the cortical markings and transferred to paper. The limitations of each area were carefully noted from a study of the sections and were indicated on the tracings, from which they were transferred to the drawing. The boundary between area 4 and area 6 was arbitrarily placed at the last gigantic ganglion cell. The external pyramidal layer in area 6 is somewhat wider and contains more and larger pyramidal cells than the corresponding layer in area 4. The boundary between area 4 and area 3 is sharp. Area 3 has well developed external and internal granular layers and a narrow internal pyramidal layer, which contains no large ganglion cells. The boundary between area 6 and the prefrontal cortex is not easily determined. Areas 8 and 9 have a well developed internal granular layer. In general, the formation of area 4 and area 6 remained the same in the various species studied. The most striking varia-

tion is progressive narrowing of the oral portion of area 4. In the monkeys this area is of almost constant width; in the baboon the most oral portion narrows sharply, and in the chimpanzee and orang-utan the narrowing is still more pronounced, although not as marked as in man.

FRASER, Philadelphia.

VOLUMETRIC MEASUREMENTS OF THE CONTRACTILE ELEMENTS OF THE RODS AND CONES. CLINTON M. OSBORN, J. Comp. Neurol. **63**:1 (Dec.) 1935.

This investigation was carried out to determine the nature of the contracting and elongating elements in the vertebrate retina and to study their proportions under extreme conditions. The work was begun on Fundulus, Ameiurus and Rana pipiens. The catfish, Ameiurus, was found to be most suitable, because the myoid structure when elongated is ten times as long as when contracted. Eyes were removed from catfish which had been in the light for several hours and from others which had been light adapted in various ways. The eyes were fixed, embedded and sectioned longitudinally or vertically in relation to the visual elements.

Examination of histologic preparations revealed that the myoids of rods contract more evenly than those of cones. The myoids of the rods and cones retained their respective constant volumes in all stages of contraction or elongation. Cones showed greater variability than rods in the amounts of contraction at the extremes of adaptation to dark and light. The myoid membrane was thicker during contraction than during elongation. The mechanism for the bidirectional activity of the rods and cones seems to be confined to the myoid structure. Osborn believes that darkness is as much of a stimulus as light.

ADDISON, Philadelphia.

SPECIFIC RESPONSES ELICITABLE FROM SUBDIVISIONS OF THE MOTOR CORTEX OF THE CEREBRUM OF THE CAT. JAMES W. WARD and SAM L. CLARK, J. Comp. Neurol. **63**:49 (Dec.) 1935.

In these experiments the weakest stimulus which would produce a response was used. One or more small areas were studied in twenty-four cats. Motor responses were obtained in the contralateral forelimb from an area extending over the lateral two thirds of the anterior sigmoid gyrus and over a part of the posterior sigmoid gyrus, near the lateral end of the cruciate gyrus. Responses in the contralateral hindlimb were obtained over most of the medial two thirds of the posterior sigmoid gyrus and a part of the medial portion of the anterior sigmoid gyrus.

Smaller areas which produced specific movements dependent on a small amount of muscle were found. These small areas were relatively constant in position and in their relation to the more permanent landmarks of the brain. Specific areas for rhythmic movements of the forelimb were found which were different from the areas which would produce the separate movements into which the rhythmic movements could be analyzed. At some points it was possible to obtain movements from both contralateral limbs by stimulating a single point. The depths of the various sulci were not explored. Ward and Clark believe that their results, although not in agreement with those of previous investigators, could be repeated by other experimenters under like conditions.

FRASER, Philadelphia.

THE HISTOLOGY OF THE PARAPHYSIS OF AMBLYSTOMA. PAUL GIBBONS ROOFE, J. Morphol. **59**:1 (March) 1936.

The paraphysis of adult Amblystoma tigrinum is a highly vascular structure derived by evagination from the anterior wall of the velum transversum and lying between the posterior poles of the cerebral hemispheres. It is composed of low columnar ependymal epithelium forming tubules which end blindly but which are continuous with one another at a common mouth communicating with

the third ventricle. Between the tubules freely anastomosing venous sinusoids, made entirely of endothelium, form a complicated rete. The blood supply to the paraphysis is entirely venous.

Mitochondria were abundant in the paraphysis of one female just previous to laying but were very sparse in all other specimens. The Golgi apparatus and many large crystalloids were observed localized between the nucleus and the ventricular end of the cell. Intercellular spaces and intercellular canals were brought out by the use of appropriate stains. Particles within the intercellular spaces which stained with acid fuchsin were more abundant toward the sinusoids than toward the cavities of the paraphysial tubules. The intercellular canals were not seen to communicate with either the sinusoids or the tubules.

WYMAN, Boston.

THE CONDUCTION PATHS OF THE INFRATHALAMIC REGION: II. AFFERENT AND EFFERENT PATHS. G. ROUSSY and M. MOSINGER, Encéphale **30**:613, 1935.

Topographically and embryologically, the infrathalamic region can be divided into: (1) the preoptic zone, (2) the hypothalamus, subdivided into anterior and posterior segments, the latter including a mamillary and an extramamillary portion, (3) the subthalamus, (4) the pallido-entopeduncular zone and (5) the parolfactory zone, made up of the substantia innominata of Reichert. Physiologically, the infrathalamic region comprises three groups: (1) olfactory—the preoptic, mamillary and parolfactory zones; (2) motor—the subthalamus and the pallido-entopeduncular zone, and (3) vegetative effector—the anterior portion of the hypothalamus and the extramamillary portion of the posterior part of the hypothalamus. Roussy and Mosinger have studied the connections of the preoptic and the parolfactory zone elsewhere. The afferent and efferent paths of the remaining structures are described in this article.

Among the corticohypothalamic fibers of rhinencephalic origin, Roussy and Mosinger observed in man and in the dog fibers passing from the fornix to the periventricular gray substance of the anterior portion of the hypothalamus, intermingled with fibers of the dorsoventral portion of the periventricular system. There were also fibers from the fornix to the principal filiform nucleus, the tangential nucleus and the anterior and inferomedial segments of the fundamental grisea of the anterior portion of the hypothalamus. Short direct fibers from the amygdala, known to exist in rodents, were shown in man. They constitute a direct amygdalotangential bundle. The important rôle of the rhinencephalon in vegetative activities, both in man and in animals, is stressed.

Direct connections existing between the central sensory paths and the vegetative hypothalamus explain the reactions of the hypothalamic animal. An example of these direct sensory connections is the retinotangential bundle. One of the reflexes mediated by this bundle is the hypophysial secretion of a melanophoric substance following visual stimulation. These fibers were found in man and in the dog. They had previously been observed in the pigeon and the squirrel.

Roussy and Mosinger confirm the opinion of Forel, Wallenberg and Ramón y Cajal that the mamillary peduncle is an afferent structure and ends only partly in the mamillary body, the rest of the fibers going to the hypothalamus. Its origin is double—from the medial fillet and from the tegmentum. Roussy and Mosinger name these two parts the bulbohypothalamic and the tegmentohypothalamic bundles, respectively. They are distinct up to the midbrain, where they join to form the mamillary penducle. The lateral part of the peduncle sweeps past the mamillary body and ends in the tuber cinereum. The fibers to the tuber can be followed easily in the dog in sagittal sections through the lateral mamillary nucleus. Independent of the mamillary peduncle, there are fibers which leave the medial fillet just before the fillet reaches the thalamus and which can be followed into the zone of the posterior nucleus of the hypothalamus. These fibers are termed the dorsal bulbohypothalamic fibers.

The majority of the afferent fibers of the mamillary body are not, as is generally stated, olfactory but are fibers from the central paths of general sensation.

Of the numerous efferent paths of the infrathalamic region, two groups have been studied particularly by the authors. The hypothalamosensory fibers include fibers to the retina, the presence of which was demonstrated in man, and hypothetic, but highly probable, fibers to the olfactory receptors. The fibers to the retina, coming from the tangential nucleus, probably regulate the excitability of the retina and supply trophic innervation to the retina and the choroid. This would explain the relative frequency of pigmentary retinitis in association with hypothalamic lesions. The visual hallucinations which occur in lesions of the hypothalamus and the mesencephalic tegmentum may be explained by chronaxic changes caused by alterations of the tangentioretinal path.

The hypothalamohypophysial bundle, so named by the authors, was first described by Cajal, in 1901. It has since been observed in various animals, both fish and mammals, and was described by Roussy and Mosinger in man and the dog in 1932. Its origins are: (1) the paraventricular nucleus of the anterior portion of the hypothalamus, (2) the inferior periventricular nucleus, or nucleus of the infundibulum, (3) the anterolateral segment of the tangential nucleus, (4) the inferomedial segment of the tangential nucleus, or accessory medial tangential nucleus, (5) the posteromedial segment of the tangential nucleus, (6) the retrochiasmatic segment of the tangenital nucleus, (7) the nuclei proprii of the tuber, in man, and the inferomedial nucleus of the anterior portion of the hypothalamus and (8) probably the hypothalamomamillary nucleus, the ovoid nucleus, the medial nucleus of the preoptic zone and the vegetative nuclei of the thalamus. All these fibers concentrate in the infundibulum, where they undergo a partial decussation, which was demonstrated by Laruelle. In the stalk of the pituitary gland most of the fibers are in the posterior segment, where almost all the tangentiohypophysial and paraventriculohypophysial fibers are located. Some hypophysiopetal fibers are also present in the anterior segment, notably, the tuberohypophysial fibers. The fibers are all parallel to the long axis of the stalk. They cross perpendicularly the blood vessels from the pars tuberalis. Beneath the ependymal recess, the fibers spread out fanwise into the posterior lobe of the hypophysis, where they form compact bundles. Some fibers can be followed into the pars intermedia. Some fibers reach the pars tuberalis, either directly from the stalk or by a recurrent route from the posterior lobe. These fibers are either medullated, chiefly those from the paraventricular and tangenital nuclei, or nonmedullated, chiefly those from the nucleus of the infundibulum and from the fundamental grisea. No definite end-organs are seen, and the fibers do not seem to come in contact with the secretory cells, except in the glandular islets of the pars nervosa, which are penetrated by the nerve fibers.

The physiologic rôle of the hypothalamohypophysial bundle is obscure. The possibility of a peculiar viscerosensory (endocrinosensory) function must be considered. The hypophysis is the only known viscus innervated directly by central vegetative formations without the interposition of ganglia. The hypothalamohypophysial system cannot be classified as either sympathetic or parasympathetic. The infrathalamic region is connected with almost all levels of the central nervous system.

LIBER, New York.

Physiology and Biochemistry

THE SUMMATION OF OLFACTORY IMPULSES FROM THE TWO OLFACTORY MEMBRANES AND ITS PHYSIOLOGICAL SIGNIFICANCE. CHARLES A. ELSBERG, Bull. Neurol. Inst. New York **4**:544, 1936.

The results of recent olfactory tests devised by Elsberg show that there are: (1) summation of impulses in birhinal smell; (2) summation of impulses to a lesser degree when the olfactory receptors of one side of the nose are stimulated by an odor and those of the other side by air, and (3) a definite relation between the strength of the stimulus and the duration of time during which summation occurs. Study of summation of impulses from the two olfactory membranes is of value for the understanding of the physiologic relation between the strength of

an olfactory stimulus and its effect on the receptor cells in the olfactory centers. It explains the cause of prolongation of fatigue on the affected side of the brain in cases of tumor within the substance of one cerebral hemisphere.

KUBITSCHEK, St. Louis.

THE CHEMISTRY OF CRYSTALLINE SUBSTANCES ISOLATED FROM THE SUPRARENAL GLAND. HAROLD L. MASON, CHARLES S. MYERS and EDWARD C. KENDALL, J. Biol. Chem. **114**:613, 1936.

The crystalline substance isolated in 1933 from adrenal glands by Kendall and his associates has not proved to be the active principle of the cortex, as they believed. Subsequently, several other crystalline substances have been separated, with physical and chemical properties similar to the original crystalline compound. No report is made of their physiologic properties. It is evident from this communication that the authors were previously misled by inadequate biologic testing, a difficulty which has now been overcome.

PAGE, New York.

THE CARBOHYDRATE METABOLISM OF BRAIN: II. THE EFFECT OF VARYING THE CARBOHYDRATE AND INSULIN SUPPLY ON THE GLYCOGEN, FREE SUGAR, AND LACTIC ACID IN MAMMALIAN BRAIN. STANLEY E. KERR and MUSA GHANTUS, J. Biol. Chem. **116**:9, 1936.

Kerr and Ghantus have reexamined the question of the relationship of glycogen, free sugar and lactic acid in brain by much improved methods. Brain was found to resemble muscle in its ability to retain glycogen more tenaciously than liver. The glycogen content of the normal cerebrum was found to lie within the range of from 77 to 150 mg. (average 98 mg.) per hundred grams in well fed, fasting dogs and of from 70 to 99 mg. (average 82 mg.) in rabbits. Fasting, overfeeding, infusion of dextrose with or without insulin, phlorhizin poisoning followed by injection of epinephrine and pancreatectomy all failed to cause significant changes in the glycogen content of the brain. Overdosage with insulin caused a marked decrease in the glycogen in dogs and rabbits.

The free sugar content of brain in animals used as controls varied from 35 to 75 mg. per hundred grams, in rabbits, and from 45 to 86 mg., in dogs. Lowering the blood sugar by phlorhizin poisoning or by insulin caused a corresponding decrease in the amount of sugar in the brain. Hyperglycemia caused by pancreatectomy or administration of dextrose caused a rise of sugar in the brain. The free sugar content of brain was constantly lower than that of blood, except in extreme hypoglycemia due to insulin. Neither lactic acid nor phosphocreatine of brain was affected significantly by any of the experimental conditions.

PAGE, New York.

A CONSIDERATION OF THE BIOLOGICAL FACTORS INFLUENCING THE RADIOSENSITIVITY OF CELLS. P. S. HENSHAW and D. G. FRANCIS, J. Cell. & Comp. Physiol. **7**:173 (Dec.) 1935.

The purpose in this investigation was to determine whether a close association exists between sensitivity to radiation and rate of growth, mitotic activity, rate of respiration and water uptake and whether changes in sensitivity to radiation may take place independently of such commonly observed biologic processes. Measured doses of radiation were administered to wheat at different stages during early development and under different biologic conditions. Subsequent growth of the organisms was then measured under conditions of control to determine the relative retarding power of the radiation when given to organisms the biologic characteristics of which differ. No close relationship exists between sensitivity to radiation and the biologic processes studied. The coexistence of greater biologic activity and greater sensitivity to radiation in organisms is not firmly established.

CHORNYAK, Boston.

THE RELATION OF NERVES TO CHROMATOPHORE PULSATIONS. GEORGE HOWARD PARKER and SYLVIA MILLS PUMPHREY, J. Cell. & Comp. Physiol. **7**:325 (Feb.) 1936.

Pulsations may be excited in the melanophores of Fundulus from which all traces of nerve elements have been removed by a degenerative operation. Such movements, then, are not necessarily dependent on nerve. They must depend, therefore, on the direct effect of the activating agents on the melanophores themselves. A pulsation never extends to the full limits of normal activity but reaches at most from full concentration of pigment to only partial pigment dispersion.

CHORNYAK, Boston.

PHOSPHOCREATINE AND LACTIC ACID CHANGES IN POTASSIUM CHLORIDE CONTRACTURE OF FROG MUSCLES IN ACID SOLUTIONS. S. R. TIPTON, J. Cell. & Comp. Physiol. **7**:433 (Feb.) 1936.

Frog muscle in solutions buffered at a p_H of 6 shows contracture, increase in the rate of oxygen consumption and hydrolysis of phosphocreatine, but no accumulation of lactic acid until the concentration of potassium in the solution reaches 80 mg. per hundred cubic centimeters. This glycolysis probably provides the energy for the increased resynthesis of phosphocreatine which is observed at this concentration. These conclusions were confirmed by measurements of the absorption and evolution of carbon dioxide, the effect of potassium chloride being an increased absorption of carbon dioxide followed by evolution as the formation of lactic acid developed. At p_H 6 there is more hydrolysis of phosphocreatine under anaerobic than aerobic conditions. In the presence of oxygen there is resynthesis of phosphocreatine, even though there is no increased formation of lactic acid.

CHORNYAK, Boston.

TEMPORAL AND SPATIAL SUMMATION OF EXTRINSIC IMPULSES WITH THE INTRINSIC ACTIVITY OF THE CORTEX. S. HOWARD BARTLEY, J. Cell. & Comp. Physiol. **8**:41 (April) 1936.

Electrical responses of the optic cortex to both photic stimulation of the retina and electrical stimulation of the optic nerve were studied by paired, triple and indefinitely repeated stimuli. The size of the response to the second of two equal shocks or flashes is determined by the interval between the two, the first stimulus synchronizing a number of the elements and instituting a cycle of the same proportions as the one discovered to exist spontaneously. The interval between the second and third shock necessary to elicit a threshold third response is determined by the interval between the first two in conjunction with the activity cycle of the elements involved. The cortex may respond to a train of rapidly repeated stimuli after a short period of adjustment, in which apparently some elements come to respond to one stimulus and others to the next, and so on, until the already activated elements recover sufficiently to repeat the process. The cortex can respond vigorously to an "on" stimulus which follows an "off" stimulus with an interval at least as short as 10 sigmas. Specific cortical points were located for the respective retinal areas. As measured, the cortical representation of specific points of the retina is diffuse.

CHORNYAK, Boston.

THE ACTION POTENTIAL OF THE SUPERIOR CERVICAL GANGLION. J. C. ECCLES, J. Physiol. **85**:179 (Oct. 26) 1935.

Langley in 1900 strongly upheld the view that sympathetic ganglia act solely as relay stations in the efferent sympathetic pathway. Further, he showed (1904) that there is no evidence that commissural fibers form functional connections between ganglion cells of similar function within a ganglion, and the absence of such commissural or internuncial neurons was demonstrated histologically. However, Langley was careful not to infer that ganglion cells receive branches from

but a single preganglionic fiber. More recently the physiologic function of the sympathetic ganglion has been studied mainly by the three following technics: (1) comparison of the effects on the end-organ (nictitating membrane) of preganglionic and postganglionic stimulation; (2) comparison of the preganglionic and postganglionic electrical records, (3) and perfusion of sympathetic ganglia.

All the work done is in general agreement with Langley's conception of the sympathetic ganglia as mere relay stations, and physiologic and histologic investigators have both gone further than Langley and expressed the belief that each preganglionic fiber ends in relation with its own specific group of ganglion cells, an impulse in the preganglionic fiber setting up a discharge from each of the ganglion cells. Such a preganglionic-postganglionic connection is, under normal conditions, functionally equivalent to mere branching of the preganglionic fiber. A more complex behavior of ganglion cells is suggested, however, by the experiments of Boshamer, which seem to indicate that an autonomous activity of ganglion cells develops several hours after section of the preganglionic fibers.

The present paper describes an attempt to investigate further the physiologic behavior of the sympathetic ganglion by analyzing the ganglionic action potentials produced under various conditions and by comparing them with the preganglionic and postganglionic action potentials. Almost all experiments were performed on cats decerebrated under deep ether anesthesia, sufficient time being allowed for the effect of the short anesthesia to pass off. The remaining experiments were performed on Belgian hares under pentobarbital sodium anesthesia, control experiments on cats showing that this anesthesia did not produce appreciable changes in the behavior of the ganglion.

Eccles found that the main potential wave which a preganglionic volley produces in the superior cervical ganglion is a spike potential set up by impulses discharged from the ganglion cells along the postganglionic fibers. In addition, a late negative potential wave and a still later positive wave are produced in the ganglion, but they differ from the spike potential both in their relatively slight spread along the postganglionic trunk and in their greater sensitivity to the action of nicotine.

The spike potential wave is composite, being usually separable into four component waves (confirming the statement of Bishop and Heinbecker), called S_1, S_2, S_3 and S_4, each of which corresponds to a discrete group of ganglion cells supplied apparently exclusively by its own group of preganglionic fibers. It is probable that the four groups subserve different functions and that this should be the basis of their ultimate differentiation, but in the present study this has been investigated no further than in confirmation of the statement of Bishop and Heinbecker that the S_1 group is distributed to the nictitating membrane, Müller's muscle and the dilator muscle of the pupil. Presumably, this composite functional character is related to the frequently observed division of the S_1 wave into two or three partly separated subsidiary waves. Bishop and Heinbecker further showed that S_2 is largely vasoconstrictor and pilomotor, while S_3 and S_4 are of still unknown function.

ALPERS, Philadelphia.

ALL OR NONE LAW; BLOCK; ALTERNANS, BIGEMINI AND ALLIED PHENOMENA AS PROPERTIES OF THE SPINAL CORD. E. VON HOLST, Arch. f. d. ges. Physiol. **236**:515, 1935.

In certain fishes (Sargus and Labrus) rhythmic movements of the fins appear after transverse section of the medulla oblongata. The rhythm of one, e. g., a dorsal, fin may be influenced by the dominant rhythm of another, e. g., a pectoral, fin. This relationship is called relative coordination. One may observe a periodic intermission in the movements of one of the pectoral fins. This phenomenon is called "block"; it is explained by the assumption that the automatic rhythmic production of a stimulating substance is interrupted. Since either a maximal or no effect is observed, von Holst infers that the all or none law is valid here. In some cases alternation of strong and weak contractions was observed ("alternans" phenomenon). Von Holst assumes that this phenomenon is due to changes in

the excitability of the motor cells or of the muscle. The rhythm at rare intervals is disturbed by the appearance of "extrasystoles" which are not followed by a compensatory pause. If such extra rhythms appear periodically, "bigemini" are produced. They differ from the "alternans" phenomenon in that two beats are close together and are separated by a longer interval from the next two beats. By stimulation of peripheral receptors the rhythm may be increased or inhibited; pressure on the back, for instance, may suppress the rhythm, and pressure on ventral parts may increase it.

SPIEGEL, Philadelphia.

LABYRINTHINE REFLEXES AFTER THE OTOLITHIC MEMBRANES HAVE BEEN THROWN OFF. T. HASEGAWA, Arch. f. d. ges. Physiol. **236**:589, 1935.

Magnus and de Kleyn found that the postural reflexes were abolished after throwing off the otolithic membranes in guinea-pigs by centrifugation, while the acceleratory reflexes were still present. Subsequent experiments of Hasegawa, de Kleyn and Versteegh showed, however, that the tonic (postural) reflexes of the labyrinth are preserved after the otolithic membranes have been thrown off. The results of Hasegawa differ from those of de Kleyn and Versteegh in regard to the reflexes on linear accelyeration (jrogression movements). These reflexes were still present in the experiments of de Kleyn and Versteegh on guinea-pigs after violent centrifugation, while they were not noted by Hasegawa after this procedure. Hasegawa repeated the same type of experiments in frogs and corroborated his observations in guinea-pigs. He explains the results of the Kleyn and Versteegh by the assumption that these authors did not succeed completely in throwing off the otolithic membranes.

SPIEGEL, Philadelphia.

INFLUENCE OF HIGH PRESSURE ON THE ACTION CURRENTS OF MUSCLE AND NERVE. U. EBBECKE and H. SCHAEFER, Arch. f. d. ges. Physiol. **236**:678, 1935.

The influence of high pressure on the action currents of nerve and muscle was studied with a cathode ray oscillograph. Maximal action currents of nerves are lowered; the conductivity drops, and the excitability of the nerve is increased. The after-potential is increased, and rhythmic reactions to single stimuli appear. The action currents of muscles are always lowered, even if slighter pressure is applied than to the nerves.

SPIEGEL, Philadelphia.

Neuropathology

SPINAL SYMPTOMS WITH LYMPHADENOMA. I. M. ALLEN and J. O. MERCER, J. Neurol. & Psychopath. **17**:1 (July) 1936.

Involvement of the central nervous system in the course of Hodgkin's disease is not uncommon. The various methods by which symptoms of spinal disease are produced are: (1) lymphadenomatous invasion of the vertebral column, resulting in erosion and dislocation of the spine with compression of the cord; (2) infiltration of the epidural space (most common); (3) extension into the subdural space; (4) involvement of the nerve roots; (5) obstruction of the blood vessels, resulting in degeneration of the cord, and (6) inflammatory and degenerative changes in the cord and its membranes without extension of lymphadenomatous tissue. Allen and Mercer report two cases which fall into the last indefinite group. In both cases there were pronounced clinical symptoms of myelitis but, whereas in case 1 the process was acute, in case 2 it followed a prolonged chronic course. The changes in the cerebrospinal fluid in both cases suggested an inflammatory condition. Pathologically, this was confirmed in case 1 by acute changes in the spinal cord consisting of edema, congestion, moderate infiltration with small round cells and changes in the nerve cells. In case 2 there were no demonstrable changes in the cord. The most important feature was the disparity between the severe clinical manifestations and the slight pathologic changes. Experimentally, intracerebral

inoculation of rabbits with emulsions of lymphadenomatous tissue have produced generalized encephalomyelitis. This follows the injection of active lymphadenomatous tissue, whereas with a less active substance only a chronic condition of neurologic disability is produced, without demonstrable structural changes in the cord. An encephalitogenic agent in lymphadenoma is assumed, but it is not known whether this is a specific toxic activity or is due to the action of a filtrable virus. The striking similarities between the effects in the experimental animal and those in the cases reported support the view of the presence of a pathogenic agent in lymphadenoma which is capable of producing lesions in the central nervous system.

N. MALAMUD, Ann Arbor, Mich.

MEDULLARY ALTERATIONS IN A CASE OF CHRONIC ALCOHOLISM. V. DIMITRI, Rev. neurol. de Buenos Aires **1**:3 (July-Aug.) 1936.

Dimitri reports a case of chronic alcoholism with interesting nerve lesions. The cause of death was cerebral hemorrhage. The important lesions involved the spinal cord, where there was degeneration of the posterior and lateral columns, most marked in the former and involving especially the columns of Goll. The degeneration was funicular and not systemic.

ALPERS, Philadelphia.

OCCURRENCE OF EPIDEMIC ENCEPHALITIS COMBINED WITH MULTIPLE SCLEROSIS. GERD PETERS, Deutsche Ztschr. f. Nervenh. **138**:23 (Aug.) 1935.

Attention has been called of late to the relative frequency of encephalitic symptoms in cases of multiple sclerosis. The difficulty of differential diagnosis, especially in the early stages of acute multiple sclerosis, has been pointed out by Guillain, Marburg and Redlich. However, none of the authors assumed the presence of a combination of the two diseases. Peters reports a case which seems to indicate that such a combination may take place.

A boy at the age of 6 suffered an attack of encephalitis, which left him with mental backwardness. Three years later a diagnosis of postencephalitic "pseudopsychopathy" was made in a psychiatric clinic. Muscular rigidity with salivation gradually supervened. Temporary paresis of the lower portion of the right arm set in, at the age of 19. The patient died, at the age of 20, of chronic parkinsonism.

There was a typical histologic picture of epidemic encephalitis. The substantia nigra showed glial fibrosis, with nearly complete destruction of the myelin of the ganglion cells. There were diminution in the number of ganglion cells in the locus caeruleus and an increase in glia at the base of the fourth ventricle and in the aqueduct, all of which speaks for epidemic encephalitis. In addition, there were sharply circumscribed demyelinated areas—some periventricular, some in the white substance and some passing into the outer surface of the cortex. These recent lesions appeared to be typical of multiple sclerosis.

Although a clinical diagnosis of multiple sclerosis was hardly possible in this case, pathologically the circumscribed lesions must be considered as distinct from those responsible for the encephalitis. Peters, therefore, thinks that two distinct processes took place in this case: encephalitis followed by multiple sclerosis.

BERNIS, Buffalo.

PRIMARY MELANOSARCOMA OF THE BRAIN, NUMEROUS PIGMENTED NEVI OF THE SKIN AND EXTENSIVE NEUROFIBROMATOSIS OF THE CUTANEOUS NERVES. M. BJÖRNEBOE, Frankfurt. Ztschr. f. Path. **47**:363, 1935.

A large melanosarcoma of the right cerebral hemisphere was observed, which apparently arose from the pia mater. Numerous and extensive nevi were present in the skin; these seemed to be intimately connected with nerves, which in turn revealed changes characteristic of neurofibromatosis. The author states that the observations seem to substantiate the theory of Masson and Ewing regarding the neurogenic origin of nevi.

SAPHIR, Chicago. [ARCH. PATH.]

DIFFUSE SCLEROSIS OF THE CEREBELLUM. BRUNO KECHT and EUGEN POLLAK, Jahrb. f. Psychiat. u. Neurol. **53**:45, 1936.

Kecht and Pollak report the case of a woman aged 50 who was operated on for carcinoma of the ovary, in July 1929; after the operation radiation was employed. In May 1931 the patient began to complain of pain in the back of the head, vertigo and vomiting. The neurologic findings pointed to an expanding lesion in the left cerebellopontile angle. The lesion was thought to be metastatic. Exploration revealed no neoplasm. Although the somatic complaints improved somewhat after operation, there developed increasing dementia. Eight months later there appeared symptoms of intestinal obstruction, for relief of which the patient was subjected to an abdominal operation, during which there was observed a metastatic tumor arising from the ovary compressing the cecum. Eight days later a pulmonary embolus occurred and the patient died approximately eight months after onset of the first symptoms of intracranial involvement.

Macroscopic examination of the brain revealed no abnormalities other than a somewhat smaller left cerebellar hemisphere. Microscopic examination of the cerebellum disclosed system degeneration of the white substance of the left cerebellar lobe and a less intense, and more recent, similar pathologic process in the right cerebellar lobe, with foci resembling status spongiosus. The brunt of the pathologic process was in the dentate nuclei, in which the white substance was replaced by closely packed masses of fatty granular corpuscles; these masses were also observed around the nuclei, but in these locations they were more scattered and interspersed with islets of normal cerebellar tissue, especially in areas remote from the nuclei. In addition to these foci of compound granular corpuscles, there was considerable fascicular glial reaction in and around the dentate nuclei; although the glial reaction appeared to be of relatively recent origin and was still active, the proliferation of glia fibers was already far advanced. Beside the lesions thus far described, there were also a diffuse fatty Abbau reaction and a rich deposit of lipoid masses in the white substance. Most of these masses were not observed in the cells, and they did not invade the cortical gray matter of the cerebellum. The myelin sheaths showed no evidences of involvement.

The cortex of the cerebellar hemispheres and vermis revealed for the most part no structural changes except a few small areas in some of the lobules in which there was typical cortical atrophy with secondary lobular sclerosis. According to Kecht and Pollak, this scanty, though definite, involvement of the cortical gray matter speaks against the condition as a pure system disease. In this connection it must also be pointed out that, as a result of the intracranial operation, there developed a thick dural scar, underneath which the cortex of the cerebellar lobules appeared degenerated; this process, however, was observed only in the lobules immediately subjacent to the dural scar, so that the sclerosed regions in this part of the cerebellum were probably due to circulatory disturbances secondary to the dural scar. This process was merely an accidental observation and bears no relation to the lesions in the white substance.

The authors believe that the pathologic changes in the white substance were undoubtedly of recent origin; the disease involved the cerebellum and lasted only eight months; according to them, this is the shortest duration of sclerosis of the white substance of the cerebellum recorded in the literature. The process began abruptly. The peculiar tissue reaction in the cerebellum was associated apparently with swelling which presented the clinical picture of an expanding intracranial lesion. At the height of the symptoms suggesting a tumor, the patient was subjected to craniotomy and, although no tumor was observed, the cerebellar symptoms receded almost completely. As a result of the operative procedure, there occurred a change in the pathologic process. The decompression apparently caused an alteration in the volume of the cerebellum, so that the circulatory disturbances resulting therefrom may have changed suddenly the nature of a preexisting degenerative process. In view of this, the authors urge caution in the interpretation of the tissue reactions in the medullary layers of the cerebellum

in the case reported. First, the pathologic changes in this case do not conform to any of the changes usually observed in destruction of nerve substance. The most outstanding feature was dissociation between the lipoid content and the myelin sheath picture. The lipoid content of the white substance was unusually high, in the presence of practically normal myelin sheaths. This raises the question whether the lipoid masses were derived from the myelin or whether they were the expression of a peculiar disturbance in lipoid metabolism, in the course of which the lipoids conveyed to the nervous system were not assimilated but remained wherever they were deposited. This question cannot as yet be answered. The authors cite Scherer, who was also struck by the dissociation of the changes in the myelin sheaths and those of the glia and fat in his cases. In Scherer's cases there was disclosed severe destruction of the myelin sheaths, whereas the fat preparations showed a striking lack of lipoid products. This observer therefore expressed the belief that when histologic examination was made in his cases the phase of lipoid destruction had already been passed.

Kecht and Pollak believe that their case is of significance as far as the so-called abiotrophic myelin process is concerned, for it illustrates that lipoid destruction of the myelin sheaths occurs at a time when their structure cannot yet be recognized by the ordinary methods of investigation. They believe further that when total destruction of the myelin sheaths begins, the phase of lipoid destruction has already passed, so that in the later stages of the disease no products of lipoid disintegration can be demonstrated, even though the myelin sheath structure is still being destroyed.

From the investigation of the productive reaction of the neuroglia in their case, Kecht and Pollack conclude that there occurs a relatively rich glial production almost at the same time that lipoid destruction becomes manifest. This proliferation of the fascicular glia sets in before the destructive phase of the parenchyma has terminated. This sheds new light on glial reactions in sclerotic processes. Fascicular glial reactions apparently may occur early in sclerosing processes; they may take place before the parenchymal defect can actually be demonstrated; in this sense the sclerosing process may be regarded as a manifestation of the initial phase of the entire pathologic process. Whether this is universally true must still be left an open question. It is also noteworthy that the pathologic changes in the case reported are analogous to those observed in acute multiple sclerosis.

As to the localization of the process: The maximal development of the pathologic process in the dentate nucleus is significant because this nucleus is in close relation to the gray matter of the cerebellum, thus assuming greater topistic significance than the other parts of the white matter of the cerebellum. Whereas the cortex of the cerebellum was relatively unaffected, the total change in the white substance involved in some areas considerable variations in the form and nature of the reactions. The entire process is undoubtedly one of relatively recent disintegration of the white matter of the cerebellum, which, owing to the widespread dispersion throughout and its strict limitation to the white matter, speaks unequivocally for an early sclerosis, which the authors designate as diffuse sclerosis of the white matter of the cerebellum.

KESCHNER, New York.

MENINGEAL MESENCHYMOMA OF FOREIGN BODY ORIGIN. O. MARBURG, Virchows Arch. f. path. Anat. **294**:759, 1935.

A boy aged 15 years was operated on for the removal of an astroblastoma of the parietal lobe. Hemorrhage at the time of operation necessitated packing the wound. After recovery jacksonian seizures continued, and headache returned and became progressively worse. Five years after the first operation the patient was again operated on. At the site of the first operation there was a firm tumor of the leptomeninges that invaded the brain and could not be completely removed. The tumor contained a strip of iodoform gauze left from the first operation. Death was due to meningitis. The tumor was cellular and anaplastic; its cells were polymorphic, with a predominance of cells of the young spindle

type. Marburg discusses the relation of the tumor to the foreign body and the morphologic structure and possible origin of tumors arising in the meninges. For such a tumor the designation "meningeal mesenchymoma" or "primitive meningoblastoma" may be used, but only in a descriptive sense, since the tumor may be of mesectodermal origin.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

LIPOMAS OF THE BRAIN AND SPINAL CORD. L. KRAINER, Virchows Arch. f. path. Anat. **295**:107, 1935.

Krainer reports two cases of lipoma of the brain and tabulates these with sixty-five other cases from the literature. He mentions five others, the original reports of which were not available, and two in lower animals—one in a rabbit and one in a duck. In the tabulation the lipomas are grouped according to their location. The tumor is situated in the cisternal enlargements of the subarachnoid space, where it is closely attached to the vessels or nerves traversing the space or is attached to the choroid plexus. It may grow along the nerves or vessels into the brain or cord tissue and thus simulate infiltrative growth. It rarely presents evidence of progressive growth. It is a maldevelopment derived from remnants of the primitive meninx, by a process of heteroplastic differentiation.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

RELATION BETWEEN DISSEMINATED NONSUPPURATIVE ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS. GERD PETERS, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:356 (Aug.) 1935.

There is still much difference of opinion regarding the relation of acute multiple sclerosis and encephalomyelitis disseminata. Peters reports two anatomicoclinical studies which throw light on this question. The first case is that of a 30 year old woman who showed mental symptoms, motor and sensory aphasia, apraxia, a Babinski sign bilaterally and an unsteady gait with wide base. The ocular fundi were normal; the pupils reacted to light; the reactions in accommodation could not be tested. The spinal fluid was clear, with a pressure of 190 mm. of water and 26 cells per cubic millimeter. Four days after admission to the hospital the patient became delirious and incontinent. A week later left hemiparesis appeared, with involvement of the lower part of the face on the left; there was left hyperreflexia with a Babinski sign bilaterally, though the large toe on the left was in continuous spontaneous extension. Disturbances in swallowing appeared, and mental changes became increasingly severe.

Autopsy of the brain showed numerous lesions throughout the white substance, varying in size from that of a pinhead to that of a walnut. Most of the lesions were well outlined. The cortex was not affected. The basal ganglia were spared. Many of the lesions were in the vicinity of the walls of the lateral ventricles. The lesions were scattered equally through both cerebral hemispheres. There were a few foci in the subcortex of both cerebellar hemispheres. The brain stem showed no abnormality. The disease foci looked like areas of softening. Microscopic examination revealed incomplete demyelinization within the diseased areas. In most cases there was a gradual transition to intact and healthy tissue. In addition, there were areas of demyelinization with concentric rings of relatively intact myelin, resembling the foci of concentric sclerosis described by Hallervorden and Spatz. The smaller foci around the ventricles seemed to be related to blood vessels. The U fibers were involved. Gitter cells were seen throughout the affected areas, with perivascular arrangement in the more completely demyelinated lesions. Macroglial gliosis was present, with relatively little fiber formation. Large protoplasmic astrocytes were observed throughout. The paraventricular subependymal foci showed more gliosis. The number of axis-cylinders was markedly reduced in most foci, and those remaining showed signs of degeneration. There was little reaction in the mesenchymal tissue, except an unusual number of fibroblasts in some lesions. Nissl preparations showed many progressive glial elements. Many of these were in the process of transformation into

gitter cells. Many oligodendroglia cells and plump glia cells were also seen. These glial reactions were most marked at the periphery of the lesions. In addition, there was observed an unusual type of giant cell, previously described by Creutzfeld in a case of acute multiple sclerosis. It was a large cell, with poorly staining protoplasm and unusual intracellular structures. These structures were coccoid bodies (probably chromatin material) and vesicular structures with inclusions suggesting nuclear substance, in addition to evident karyorrhexis. Perivascular infiltration with plasma cells and lymphocytes was seen in all lesions, especially at the periphery. Such cellular infiltration in intact brain tissue was rare. In a few spots there were similar cellular accumulations in the meninges. The ganglion cells were unchanged.

The second case was that of a 49 year old woman who noted progressive numbness and weakness of the right hand, which were not in reaction to any evident circumstance. There was transitory improvement after two or three months, but the symptoms recurred. The weakness became rapidly progressive and involved the right lower limb, followed later by recurring weakness in the upper limb. Incontinence appeared. On admission to the hospital the patient was somnolent. There were weakness of the right internal rectus muscle, bilateral temporal pallor with atrophy of the optic nerve, facial and hypoglossal weakness on the right, right spastic hemiplegia with hyperreflexia and a positive Babinski sign on that side, intact abdominal reflexes, dysarthria and apathy and later restlessness and confusion. A few weeks after her admission the patient became more restless; the Babinski sign was present bilaterally, and clouding of the sensorium became more profound.

Here the anatomic observations were similar to those in the first case, except for the following differences: The corpus callosum was not involved; the U fibers were more affected, and the periventricular foci were particularly striking. There were no foci of concentric sclerosis, and the production of glia fibers was less marked. The giant cells of Creutzfeld were present, though not as numerous. Perivascular infiltration was less marked; there were no plasma cells or lymphocytes outside the foci in this case; a large patch in the cervical region of the cord involved the gray and the white matter indiscriminately.

The localization of the foci of demyelinization in these cases corresponds to that in classic cases of multiple sclerosis. The fibrosis noted in one of the cases, due to mesenchymal proliferation, is occasionally seen in multiple sclerosis. Jakob and Doinikow, Biondi and Peters have seen this type of tissue reaction in cases of multiple sclerosis. Cystic formation in foci of multiple sclerosis is distinctly rare and is usually due to other causes. Most lesions in the cases reported were not clearly demarcated from intact cerebral substance. This is unusual, though not unknown, in multiple sclerosis. The axis-cylinders may be destroyed in multiple sclerosis. They are usually only relatively intact. Fat stains showed changes identical with those of multiple sclerosis. Absence of production of glia fibers is not against a diagnosis of multiple sclerosis; these fibers may be absent or sparse in the early stages of the disease. The giant cells of Creutzfeld have not been observed by other investigators. The massive glial response and perivascular infiltration present in these cases are seen in disseminated sclerosis.

The anatomic picture differed from that of multiple sclerosis in the following respects: The large lesions had a spongy appearance; many of the disease foci were not well circumscribed but merged gradually into the surrounding tissues; the breaking down of neural parenchyma was unusually extensive, and typical sclerotic plaques were absent. Such an intense glial reaction with the peculiar giant cells is not seen in multiple sclerosis. The relatively rapid course without remissions, as well as the seriousness of the clinical picture at the onset, differentiated clinically the disease in these cases from disseminated sclerosis.

A strict anatomic and clinical separation of acute disseminated encephalomyelitis and multiple sclerosis is not possible with the present status of knowledge of the nature of these conditions. Until more is known about the etiology of these diseases, it is unwise to consider them as manifestations of the same

disease process. There are enough clinical and anatomic grounds on which to differentiate them, in spite of the fact that atypical cases may occasionally be difficult to classify. In the two cases reported here typical plaques were not shown. It is possible that if the patients had survived, more typical changes might have appeared. Peters objects to the terms acute multiple sclerosis and malignant sclerosis, for no sclerosing processes are demonstrable. He favors the designation nonsuppurative disseminated encephalomyelitis.

SAVITSKY, New York.

Psychiatry and Psychopathology

THE RELATION BETWEEN INSANITY AND MARITAL CONDITION. FREDERICK J. GAUDET and ROBERT I. WATSON, J. Abnorm. & Social Psychol. **30**:366 (Oct.-Dec.) 1935.

Insurance statistics show married persons live longer than single ones. Many authors attempt to explain this by saying that great numbers of persons who remain single do so because of social and sexual maladjustment and latent psychopathic tendencies. Since some authors have been inclined to explain the difference in the incidence of insanity in the married and the unmarried by presuming a greater frequency of syphilis among those who have not married, Gaudet and Watson have attempted to obtain specific facts on which to base conclusions from a study of patients at the time of their first admission to the New Jersey State Hospital at Greystone Park.

It was found that there is a greater frequency of insanity among the single, the widowed and the divorced than among the married. The difference in the incidence of insanity between the widowed and the married and between the divorced and the married is greater than between the single and the married. The conclusion is drawn that predisposition to insanity is not the only factor in explaining the differences. Widows show a greater incidence of insanity because, according to statistics, widows are older than married women and, hence, are subject to the psychoses associated with late middle life and old age. One of the most important findings in the study of patients on first admission was that psychoses due to alcohol and syphilis are not more frequent among divorced and single persons than among married persons. Hence, these two causes cannot be said to be factors explaining the higher incidence of insanity among the unmarried than among the married.

WISE, Howard, R. I.

PRIMAL SCENE, PLAY, AND DESTINY. GUSTAV HANS GRABER, Psychoanalyt. Quart. **4**:467, 1935.

Psychoanalysis finds that play gratifies simple wishes, averts conflicts, repetitively reactivates old traumas, and makes manifest in overt behavior reaction formation, identification, introjection and projection. Graber presents material from the analysis of a woman aged 33 to show the relationship between an early infantile trauma (the primal scene), play and her later destiny. As a child, the patient did not play with others and could not bear to see others play, being a frank "spoil sport." She had been thoroughly spoiled, slept in her parents' bedroom and spent each night crying until they took her up or took her into their bed. This attention ceased after the birth of a brother when she was 3, and of a sister, when she was 4 years old. She supplied her need for love by frequent illnesses and, when well, behaved at night in an insufferable manner, demanding either to be taken into her parents' bed or to be put on the pot, where she would sit for hours and do nothing. The parents transferred her to a room of her own, which made her feel more rebuffed.

She had overheard and seen parental intercourse, and this sight had produced vivid and constant imaginations. Therefore when she heard any noise from their

bedroom, she thought they were playing an interesting game from which she was excluded and felt an intense need to retaliate and to prevent their playing. The compulsion to disturb others with every means at her disposal became part of her character and life task. The impulse to disturb was transferred to all persons and animals in her neighborhood, so that when she saw persons agreeably occupied she rushed between them like a fury. During a visit to friends she learned that the boy slept with his mother and the girl with her father. She thought they did what her parents did and, being seized with hate, rage and envy, invented a new game in which she made the boy chase the girl over and under the bed while she stood in the bed with a whip, like an animal trainer, constantly urging them on but never permitting the boy to catch the girl. This game came to an unhappy end. The mother of the children insisted that the patient eat a piece of bread which smelled sour, just as she was leaving. The smell reminded the patient of urine, and she thought that the woman or her husband had urinated on the bread in order to get rid of her because they did not approve of the game. She vomited violently and continued to do so every day thereafter. She regarded the woman's insistence that she eat the bread and the vomiting as a punishment for her naughty game and also for her wish, already repressed, that her father (or mother) would urinate in her mouth—the bread which she fancied smelled of urine being a substitution for the father's penis.

From this point, her intolerance, imperiousness and aggressiveness, as well as her symptoms, increased, and in this behavior it was as though she had really swallowed her father's penis. The fear that this had happened and that it must be removed seemed the basis for her later desire to have operations, i. e., to have "something cut out of her." At the table she was afraid of choking but, at the same time, became more and more greedy and envious of her brother's and sister's food. She would not permit the father and mother to sit together. The only games she took pleasure in were those in which she ruled, tormented, separated and disturbed other children. Always, she was the dominant person, thus identifying herself with her father in the primal scene. She was cruel to animals—even to the point of killing them. Quite early, she was obsessed by a fear that she would have to kill some one but fled from this idea.

In her love affairs of adolescence—usually homosexual, because of her marked identification with her father—she loved not for the sake of love but for the sake of wrecking the love affair of some one else. Her adult heterosexual affairs were the same, and when she married, she dominated and tormented her husband, was frigid and had all her old childhood symptoms.

Throughout her preanalytic life, her one relation to the world was, in her own words: "Life is a game that has to be broken up." She did not want to play the game unless she could maintain her superiority. Her neurosis—an unclear mixture of compulsive, hysterical and actual hypochondriacal character traits—enabled her to continue to function as she had as a child. Through analysis, she was enabled to be freed from her behavior, which had been imposed on her, almost as a fate, through her reactions to the primal scene. PEARSON, Philadelphia.

SCHIZOPHRENIA AND PROLONGED NARCOSIS. ANDRÉ FAVRE, Encéphale **31**:196, 1936.

The method of prolonged narcosis, first used by Kläsi in 1920, was applied by Favre to sixteen patients with schizophrenia. The drugs used were diethyl-diallyl barbiturate of diethylamine intramuscularly, dial by rectal drip, phenobarbital by enema, morphine sulfate and scopolamine hydrobromide. Adjuvant medication to combat possible vomiting, pulmonary infection and cardiac weakness may be necessary. For cardiac weakness, camphor and digitalis are recommended. The use of coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamide) should be avoided, as it interferes with sleep. Counterindications are acute febrile disease and cardiac decompensation. The chief complications are infections of the respiratory tract, reactivation of tuberculosis, cardiac collapse, epileptiform con-

vulsions, vomiting, erythema and other manifestations of anaphylaxis or intolerance to the drug. On the appearance of any of these conditions, narcosis should be interrupted at once. The schizophrenic patients to be selected for this treatment are those whose previous character is favorable and who are sufficiently intelligent to understand what is expected of them. The patients who reacted most unfavorably to narcosis were those of low intelligence or the frankly feebleminded. The treatment acts largely through psychotherapy, which must be applied judiciously when the patient awakes. He should awake in a new environment and perhaps be attended by a new physician. Suicidal ideas disappeared almost consistently. Of the sixteen patients treated fifteen had catatonia and one hebephrenia. Five were cured, five greatly improved and three only temporarily improved; the condition of two remained stationary, and that of one became aggravated.

LIBER, New York.

A CASE OF PURE INTERMITTENT CATATONIA LASTING TWENTY-FOUR YEARS. H. DAGAND, Encéphale **31**:293, 1936.

After severe phlegmon of the hand and amputation of one finger, a man aged 25 became depressed and anxious, had delusions of persecution and experienced threatening auditory hallucinations. He attempted suicide several times. Occasionally he fell to the ground, rigid and motionless for a short time, as in the hysteriform, cataleptic attacks described by Claude and Baruk. After fugues and attacks of violence and furor, he was committed to a hospital for mental diseases. Here, irregular periods of delusion, confusion, hallucinations, anxiety and excitement alternated with apathy, depression and semistupor. From the age of 39 (1921) to the present, the disease entered a new phase, which remained unchanged. It consisted of typical attacks of Kahlbaum's catatonia, lasting from two weeks to four months. The length of the free intervals was irregular but never exceeded one month. During the attacks the patient assumed bizarre attitudes. At times he was agitated or appeared to listen to voices and replied to them with cries and insults. He spoke little, and only in incomplete, stereotyped phrases. At times he was negativistic and violent. The skin was pale and dry. The attacks began and ended suddenly. During the intervals the patient seemed mentally and emotionally normal, except for a slight intellectual deficiency. There was no evidence of progressive mental deterioration. The case was undoubtedly one of catatonia, as described by Kahlbaum, and not one of schizophrenia or manic-depressive psychosis. The striking features in the case were the relatively brief duration of the attacks and free intervals, the absence of symptoms during the intervals, the absence of dementia and the importance of hallucinations during the attack. In some of Kahlbaum's cases dementia was lacking. Baruk's theory of the toxic etiology of catatonia seems applicable here. The attacks could be explained on the basis of "toxic discharges in relation with periodic humoral modifications."

LIBER, New York.

REMARKS ON THE PROBLEM OF SYMPTOMATIC PSYCHOSES. J. GOTTSCHICK, Monatschr. f. Psychiat. u. Neurol. **91**:72 (May) 1935.

From a study of psychoses associated with carcinoma, Gottschick concludes that all mental phenomena observed in symptomatic psychoses are produced by a disturbance of consciousness plus the reaction of the preserved mental activities thereto. It is probable that the disturbance of consciousness is caused by diffuse but reversible alterations of the nerve cells of the cerebral cortex. It is not necessary to assume that special toxins produce this effect, for highly differentiated cells, such as neurons, react to injurious outside influences in general with a decrease of functional capacity. The factor of individual susceptibility plays a rôle, but the fundamental fact remains that symptomatic psychoses are based primarily on a reaction of the nerve cells to general bodily injury caused by somatic disease.

ROTHSCHILD, Foxborough, Mass.

A CLINICAL AND ETIOLOGIC STUDY OF PERIODIC ALCOHOLISM. ÖRNULV ÖDEGAARD, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:629 (Sept.) 1935.

Sixty-two (47 per cent) of 132 patients with chronic alcoholism seen at the psychiatric department of the University of Oslo, Norway, between the years 1926 and 1931 were periodic drinkers. In only sixteen of the cases was there no history of previous constant, relatively heavy drinking. In no case did a teetotaler become a periodic drinker. The bouts of drinking usually arose spontaneously and in reaction to no known external circumstance. In all cases the episodes were ushered in by distressing sensations of somatic discomfort and psychic unrest. The sufferers became restless, smoked excessively and often wandered through the streets from bar to bar, seeking companions in drink. They complained of paresthesias, abdominal discomfort, moderate thirst, hyperhidrosis and abnormal tastes. Some told of intense intrapsychic turbulence, inability to concentrate and an imperious need to break the monotony of daily routine. Insomnia soon set in and was sometimes the sole reason given for drinking. The subjects usually became dull, irritable, sensitive, taciturn and seclusive. Real depression was relatively rare, unless there had been a definite psychic trauma. At times they became tired, listless and disinclined to effort of any type. Hypomanic behavior on a cyclothymic basis accompanied the spells of inebriety in only one case. The impulse to drink does not have the features of a true compulsion, for there is usually little internal opposition to the drive.

The duration and amount of drinking vary greatly. Two main types can be distinguished, though many variants are encountered. There is the lone drinker, who shuts himself up in his room and continues to drink by himself for periods lasting from a few days to two weeks. Ödegaard reports a rare case in which the bout lasted five weeks. The second type of drinker does not drink alone but wanders from café to hotel, drinking with any one. This type of drinking may last longer, for it is often punctuated by periods of sleeping and eating. The drinking in both instances usually continues until collapse, though not infrequently dyspepsia, diarrhea and convulsions may cut the excesses short. Occasionally, lack of money prevents further indulgence, though it is astounding how the most indigent dipsomaniac manages somehow to put his hand on money to procure further drinks.

After the drinking spell is over, the drinkers usually become depressed, regretful, maudlin and sentimental, promising abstinence and dramatically forswearing inebriety. Protracted mental incapacity sometimes follows, making it impossible for them to return to work for long periods. In some cases they become tender and loving to their wives. This behavior is evidently an attempt to compensate for recent inexcusable brutality and inconsiderate behavior.

There is usually some amnesia for the period of heavy drinking, though no complete amnesia was noted in any of the author's cases. Drinkers are often concerned and anxious about their behavior during intoxication. The usual somatic signs of intoxication are not present. Coordination remains intact up to the final collapse. The affective state during drinking is one of depression and anxiety, interrupted by waves of uncontrollable irritability and rage. During the height of the intoxication one sometimes notes ideas of jealousy and reference and manic-like behavior, though no hallucinosis was noted in any case. The same pattern of behavior disturbance is usually seen in the various attacks in the same person.

The duration of the attack is usually from three to eight days, with limits varying from two days to four months. The duration is only rarely similar in the repeated episodes. Variations in duration for the same patient are usually great. The average interval between attacks is a few months, varying from a few days to a year or more. The attacks rarely recurred at regular intervals, as in one case of this series in which they came on with each menstrual period. The interval may vary in the same drinker from one week to two years. As the years go on, the periods of drinking usually become more regular and intense. The intervals of freedom become shorter rather than longer, and the periods last longer.

The personality make-up of these drinkers seems unimportant and does not play any constant and significant rôle in the predisposition to periodic drinking. There were only six patients of whom one could say with reasonable certainty that periodic drinking was related to cyclic changes in affect (two hypomanic and two so-called depressive psychopathic persons). Epilepsy in any of its protean manifestations was not evident in this series. The only two alcoholic patients who had epilepsy were constant drinkers. Eleven drinkers came from families with a positive history of cyclothymic tendencies. Nine of these were periodic drinkers. Hypomanic patients may drink during the excited phase. Three patients with endogenous depressions did not drink. This is due partly to the psychomotor retardation and to the fact that only persons with reactive depressions who are bitter and resentful toward others resort to alcohol to allay the irritability and depression. In general, one may assume reasonably that constitutional predisposing factors are present in about 10 per cent of cases as primary etiologic factors, while in about an equal number such an anlage plays a secondary rôle. Ödegaard concludes that as far as personality make-up and hereditary disposition are concerned, the periodic drinker does not differ radically from the average person with chronic alcoholism.

Psychogenic precipitating factors do not appear to be important. In most cases the drinking came on spontaneously. When psychic trauma did precede the drinking, it was not severe and unquestionably was of secondary importance in accounting for the appearance of the desire to drink. Such psychogenic factors were recorded in thirteen cases. In three cases psychic trauma played a definite rôle. In ten others it did not seem important. In two the desire for relief from boredom appeared of some moment. In none of the cases did the psychic trauma seem the only detriment.

The restlessness, anxiety and malaise which so often follow the initial drinking are often the cause of further drinking. There is a desire to relieve these symptoms. The constant prodromal restlessness and anxiety are probably conscious reactions to an existent subliminal and subconscious impulse to drink. This distressing premonitory discomfort appears only after the subconscious yielding to the desire to drink. In the periodic drinker the bridling of the craving for drink is stronger than in those with other types of alcoholism. The failure of the first glass to relieve these early mental symptoms accounts for the desire for more liquor. There is no ground for the theory that an organic basis for periodic drinking exists. There is no cogent evidence either for periodic metabolic changes or for a focal cerebral lesion as the basis for this condition.

SAVITSKY, New York.

STUDIES ON THE CONSTITUTIONAL RELATIONSHIP BETWEEN TUBERCULOSIS AND MENTAL DISEASE. M. BLEULER and L. RAPOPORT, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:649 (Sept.) 1935.

Bleuler and Rapoport studied the incidence of mental disease and the peculiarities of behavior in the parents and siblings of 100 patients in a tuberculosis sanatorium. The average age of the patients was 39 years, and all had moderately severe tuberculosis; 96 per cent had pulmonary tuberculosis. The incidence of mental disease and other behavior disorders in the tuberculous patients was somewhat less than that in subjects used as controls. There were only 2 psychotic patients—one with schizophrenia which had improved and 1 with epilepsy. There were no mental defectives; 3 patients had chronic alcoholism, and 1 conversion hysteria. Eleven of the tuberculous patients had shown defects of character and personality before the onset of tuberculosis. These patients were sensitive, irritable and jealous and showed a ready tendency to reactive depression, vegetative instability, fatigability, syncopal attacks and blushing. Hypomania and aggressiveness with antisocial tendencies were not present. The schizoid make-up was found in only 1 case.

Studies were made on 479 siblings and 200 parents of these patients. Eighteen and six-tenths per cent of the siblings died during early childhood. The incidence

of twin births among the siblings was 1:47. There was an increased mortality from tuberculosis in the relatives, as compared with figures used as controls. Forty-eight per cent of deaths of siblings over 10 years of age and 22 per cent of those of parents were due to tuberculosis. The incidence of psychoses, psychopathic tendencies, drinking and suicide in relatives of tuberculous patients was comparable to that in an average sample of the population, as determined in previous control studies in various parts of Germany and Switzerland. Vegetative instability, reactive depressions and affective lability were more frequent in relatives of tuberculous patients than in control subjects. There was no increase in the incidence of the schizoid personality in these relatives.

Tuberculous patients, therefore, from the standpoint of heredity of mental disease are as good risks as persons in the general population. In advising persons about to marry, a family history of tuberculosis is not significant from the point of view of probable transmission of schizophrenia. Schizoid persons are not more frequent among relatives of tuberculous patients than among persons studied as controls. They are found more often in families with schizophrenia, supporting the thesis of an intimate relation from the genetic standpoint of schizophrenia and this type of premorbid make-up. SAVITSKY, New York.

STATISTICAL STUDY OF NINETY MORPHINE ADDICTS. FRITZ M. MEYER, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:499 (Jan.) 1936.

This is a study of ninety addicts to the use of morphine, sixty-four (71.1 per cent) of whom were men and twenty-six (28.9 per cent) women. Forty-seven (52.3 per cent) of the number were physicians. The ages varied from 25 to 62. Most of the patients (thirty-eight) were between 30 and 40. The women were somewhat older than the men. The number of men who were not married was 33.3 per cent; 10.4 per cent were divorced. Of the sixty-six married patients twenty-seven, or 41 per cent had no children. Childless marriages of physicians who were addicts were especially frequent (fourteen or thirty). Meyer does not believe that the germ plasm of children can in any way be damaged if they are conceived or born during periods of active morphinism.

The narcotic laws have not had any significant effect on the doses of drugs taken by addicts. In only seven of twenty-four cases studied recently was the daily dose 0.2 Gm. or less. Even in these seven cases the reduction in the dose was only specious, as the reduced dose of morphine was replaced by relatively large doses of either soporifics or alcohol or both. In one case ether and nitrous oxide were used. Meyer sees no advantage in replacing one form of drug addiction by another. The value of the narcotic laws lies in the fact that they make physicians more conscious of their responsibility in the prophylaxis of drug addiction. Physicians have become more cautious in prescribing narcotics and more wary of furnishing drugs to addicts.

All but five of the addicts studied combined morphinism with the use of somnifacients and alcohol. Cocaine is being used with decreasing frequency. Laymen use phanodorm (cyclohexenylethylbarbituric acid) and allonal (allylisopropylbarbituric acid and aminopyrine). Phanodorm is used especially, because of its ability to quiet the addict, even when deprived of his drug. The free sale of soporifics should be prohibited. They should be sold only when a prescription is presented and in small quantities. Three of the persons studied were addicts for only a very short time. Addiction should be discovered and treated as early as possible. The real cause of morphine addiction lies in a fundamental inadequacy of the personality, often neurotic, which makes it impossible for these persons to handle their problems in a more normal fashion. The precipitating cause can be almost any psychic stress and strain, as well as severe pain and somatic disease. The addiction often makes it apparent that the subject has a neurosis. At times the problem of addiction can be solved only by adequate treatment of such neurotic tendencies. Psychotherapy is therefore an important adjuvant in the treatment of addiction to morphine. SAVITSKY, New York.

SCHIZOPHRENIA IN A BOY FOUR YEARS OLD. S. Z. GALATSKAYA, Sovet. psikhonevrol., 1936, no. 2, p. 117.

This case is one of a series which have been reported from the Children's Psychiatric Clinic of Tatiana Simson, in Moscow. Simson is convinced that schizophrenia can develop at the age of 2 or 2½ years. A boy aged 4 years and 3 months entered the children's psychiatric clinic because for a year he had been nervous, jumpy, antagonistic, stubborn and aggressive. Up to the age of 2½ years, he had been happy, quiet and cheerful. He liked to play with toys and was good in games involving manual dexterity. He did not play with children but, on the other hand, did not avoid them. There were no fears. He was musical and began to reproduce various tunes at the age of 1½ years. At about the age of 3 there was a marked change. He became withdrawn, overactive, confused in behavior, irritable and unable to concentrate on any task. He began to talk to himself; stammering developed and was interpreted as an attempt of the child to imitate his father, who was a stammerer. He refused to stay in his room and insisted on being in the company of adults. For no apparent reason, he began to attack children and adults. At the same time, he was unable to defend himself. His memory was excellent, and his intellectual development was progressing without delay.

When the child was admitted to the psychiatric clinic, it was noticed that he was irritable, overactive, extremely hostile and aggressive. There was much diffuse, meaningless activity. He attacked other children a great deal, for no reason. Speech was fragmentary, disconnected and rather incoherent. Neurologic examination gave negative results. The intellectual functions were intact. It was the impression of the psychiatrist that the child was living in an autistic world, with beginning disturbance of associative thinking, evidenced by choppy, disconnected productions. The boy was observed in the clinic for only three weeks. In commenting on the case, Galatskaya states that the boy's defenselessness and his complete inability to adjust himself to a new environment in spite of good intellect show that he had lost his sense of reality. The emotional factors in the case are not discussed.

KASANIN, Chicago.

Meninges and Blood Vessels

OTITIC MENINGITIS: REPORT OF A CASE IN WHICH TREATMENT WITH CONTINUOUS SPINAL DRAINAGE WAS USED. JOSEPH POPPER, Arch. Otolaryng. **24**:340 (Sept.) 1936.

The case is reported of a child aged 1 year on whom bilateral mastoidectomy was performed for otitic meningitis, with exposure of the dura. The operation did not influence the course of the disease. The temperature continued to rise. On the second day after operation there was a convulsion on the left side. There was no rigidity of the neck and no Kernig or Brudzinski sign. Hemolytic streptococci were present in the spinal fluid and the blood. The child relapsed into stupor and seemed moribund. He improved somewhat under treatment and again became stuporous. After twenty-four days the patient died of respiratory failure. At postmortem examination the pathologist could not be certain whether there was an abscess or whether simply pus exuded from the sulci of the brain.

The treatment consisted of repeated transfusions and continuous drainage of the cerebrospinal fluid by means of a ureteral catheter and cisternal puncture. The fluid assumed the character of pure pus before the patient died. As patients with streptococcic meningitis usually die in from two to five days, Popper assumed that the continuous subarachnoid drainage was an important factor in prolonging the life of the patient.

HUNTER, Philadelphia.

VARIATIONS OF THE CRANIAL VENOUS SINUSES IN THE REGION OF THE TORCULAR HEROPHILI. BARNES WOODHALL, Arch. Surg. **33**:297 (Aug.) 1936.

The clinical course, studies on the dynamics of the spinal fluid and the pathologic changes are recorded in a case in which a completely positive but false unilateral

Queckenstedt reaction was exhibited. This type of irregularity in the Queckenstedt reaction, when applied in the diagnosis of thrombosis of the lateral sinus, may be due either to external pressure on the wall of the sinus or to a major abnormality of the sinuses, as illustrated in this case. Such an anatomic abnormality has been reported in 4 per cent of cranial sinus patterns. Two other types of irregularity in the Queckenstedt reaction, the unilateral false negative and the bilateral false positive reaction, are discussed. They may have a common origin in channels of collateral circulation, either preexistent in the second type or brought into play in the presence of thrombosis in the first. GRANT, Philadelphia.

AN EPIDEMIC IN A MOUSE COLONY DUE TO THE VIRUS OF ACUTE LYMPHOCYTIC CHORIOMENINGITIS. E. TRAUB, J. Exper. Med. **63**:533, 1936.

A filtrable virus identical with that which causes acute lymphocytic choriomeningitis has been found to cause a disease in white mice. Naturally infected mice usually show no symptoms, but animals inoculated intracerebrally with sterile bouillon or other materials present characteristic symptoms. The same symptoms are produced by intracerebral injection of the virus into mice from a disease-free stock. Guinea-pigs are very susceptible and are therefore useful for detecting the virus and for neutralization tests. The disease as studied in both naturally infected and inoculated animals is discussed, and the pathologic observations are given. FROM THE AUTHOR'S SUMMARY. [ARCH. PATH.]

THE PATHOLOGIC HISTOLOGY OF LYMPHOCYTIC CHORIOMENINGITIS IN MONKEYS. R. D. LILLIE, Pub. Health Rep. **51**:303, 1936.

Lymphocytic choriomeningitis in monkeys is characterized by an almost constant irregularly distributed, pronounced lymphocytic infiltration of the choroid plexuses, sometimes accompanied by serocellular exudation into the cerebral ventricles and by an almost constant irregularly distributed lymphocytic infiltration of the leptomeninges, usually moderate, as well as by very few foci of cellular gliosis and lymphocytic infiltration of vascular sheaths in the brain and cord. The meningeal and plexus infiltration may persist for long periods after infection. Focal lymphocytic infiltration and proliferation of sheath cells occur in the spinal root ganglia.

The lungs often present congestion, serous exudation, interstitial edema, hemorrhages and perivascular lymphocytic infiltration. Pyelitis and sometimes hemorrhagic cystitis occur in a number of animals and are characterized by focal and diffuse mucosal lymphocytic infiltration and edema. Foci of coagulative to fibrinoid hemorrhagic necrosis in the liver are seen in about one fourth of the animals, and focal necroses also occur occasionally in the adrenal and parathyroid glands. Splenic congestion, a variable grade of hyperplasia of the marrow and lymph node follicles and sinus reticulo-endotheliosis are other frequent changes. Focal interstitial or perivascular lymphocytic infiltration is frequent in the kidneys, epidymis, uterus, tubes, parathyroid glands, heart, lungs and tracheal mucosa, and occasionally in the esophageal mucosa, pancreas, adrenal glands, testis, ovary and skeletal muscles. FROM THE AUTHOR'S SUMMARY. [ARCH. PATH.]

THE HEMATO-ENCEPHALIC BARRIER AND THE SYMPATHETIC NERVOUS SYSTEM. W. S. SURAT, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:438 (Aug.) 1935.

Meningeal permeability was studied in ten cases after ganglionectomy for the relief of endarteritis obliterans. The bromide method of Walter was used. In nine cases the lower limbs were involved. In these cases lumbosacral ganglionectomy was performed. In one case the cervical sympathetic ganglia were cut. In three cases the barrier was studied ten days after operation; in three, after fifteen days; in two, after three weeks; in one, after one month, and in one, after two months.

In five of the ten cases there was a significant diminution in permeability before operation. As disturbances of the vegetative nervous system are known to play a rôle in the pathogenesis of endarteritis obliterans, one can consider this altered

permeability as additional evidence of the existence of such a disorder of the autonomic nervous system. The definite lowering of the bromide quotient two months after operation indicates that this disturbance is not merely a passing reaction to operative manipulation but a persistent sequel of injury to the innervation of the apparatus which controls the barrier. SAVITSKY, New York.

Diseases of the Brain

PYKNOLEPSY. JOSEPH L. ABRAMSON, J. Nerv. & Ment. Dis. **82**:249 (Sept.) 1935.

Friedman in 1906 first called attention to a symptom complex, resembling petit mal, occurring in children between the ages of 4 and 12 years. He called it a disease entity. There is a cyclonic onset with "heaping up" or development of the maximum number of daily attacks at once. They occur from ten to one hundred times daily, persist for weeks, months or years and are not influenced by drugs. Clonic movements and urinary incontinence are rare. No biting of the tongue or frothing at the mouth is observed.

After the report of three cases of this condition, Abramson gives considerable thought to the controversy in the literature as to whether pyknolepsy is a disease sui generis or a symptomatic variation of the paroxysmal reaction, and he reaches the opinion that it is not a disease entity with a specific etiology but "a type of reaction of the nervous system." A review of the literature suggests a good prognosis, with disappearance of the attacks at puberty. In one of the author's cases four months of intensive analytic therapy resulted in no improvement.

HART, New York.

OCCURRENCE OF TRIGEMINAL NEURALGIA IN PATIENTS HAVING MULTIPLE SCLEROSIS. J. M. MEREDITH and GILBERT HORRAX, J. Nerv. & Ment. Dis. **82**:497 (Nov.) 1935.

Pain in cases of multiple sclerosis is rare. Other sensory disturbances, such as numbness and paresthesias, are comparatively common and probably occur at some period in the course of the disease in the majority of patients. The pathogenicity of pain in the face in cases of multiple sclerosis is unknown. The theory that it may be due to plaques of sclerosis in the pons, the medulla or the descending spinal root of the fifth cranial nerve is unlikely, in view of the relief obtained by injections of alcohol or avulsion of the sensory root peripheral to these lesions. It is further refuted by the reported cases of multiple sclerosis in which lesions similar in type and location were discovered and no pain in the face was noted in the history.

Twenty-five instances of concomitant trigeminal neuralgia and multiple sclerosis were encountered in a review of cases reported in the last seventeen years. In some of the patients pain preceded the symptoms of multiple sclerosis, whereas in others the reverse was true. It is probable that trigeminal neuralgia complicated by multiple sclerosis is more likely to be bilateral than the ordinary form of the disease.

Two additional cases are reported in some detail, in one of which bilateral trigeminal neuralgia occurred at different periods. Both patients were operated on, with subsequent complete relief from pain for one year. Inhalations of trichlorethylene and injections of alcohol were effective in relieving the pain temporarily in the two cases. Modern methods of treating trigeminal neuralgia associated with multiple sclerosis are as effective as in ordinary forms of the disease.

HART, New York.

CONGENITAL ARITHMETIC DISABILITY AND ACALCULIA (HENSCHEN). ERICH GUTTMANN, Brit. J. M. Psychol. **16**:16, 1936.

Guttmann believes that isolated arithmetic disability is rare. In fact, it has been maintained by some authors that mathematical skill is not a specific ability. Henschen, however, has distinguished an acalculia which is distinct from number

alexia or agraphia. Idiokinetic (distorting) and constructional (confusing of position) types of agraphia have been described, and Guttmann illustrates the relation of the constructional type to difficulties in calculating. He points out that in illiterates calculating is independent of figure writing. He found that eleven of fifteen children with difficulty in reading were normal in arithmetic. The possible relations to the visual system and to the "parietal syndrome" are discussed. Guttmann concludes that the few cases he reports "point to the interrelations being diverse." He is inclined to believe in a causal, focal anomaly of the brain, which however, does not preclude training in simple calculation by methods more circuitous than those used by the normal person. The functions found to be intact would determine the method in the individual case.

ALLEN, Philadelphia.

FAMILIAL CONGENITAL BOURNEVILLE'S DISEASE (TUBEROUS SCLEROSIS) ASSOCIATED WITH SYMPTOMS OF NEUROFIBROMATOSIS (RECKLINGHAUSEN'S DISEASE). L. BABONNEIX, M. BRISSOT, MISSET and DELSUC, Ann. méd.-psychol. (pt. 2) **94**:102 (June) 1936.

Two brothers, 6 and 4 years of age, had a severe mental defect, epilepsy and characteristic facial nevi associated with congenital anomalies of the skin resembling those observed in Recklinghausen's neurofibromatosis. The eyegrounds showed no congenital lesions. Both maternal grandparents were mentally deficient. The grandfather was alcoholic and died at the age of 41. Roentgenograms of the skulls of the patients showed intracranial calcifications which suggested tumor. The authors stress the familial occurrence of tuberous sclerosis and its coincidence with neurofibromatosis. These two cases support Bielschowsky's thesis that tuberous sclerosis and neurofibromatosis represent different aspects of the same congenital disease.

YAKOVLEV, Waltham, Mass.

REMOVAL IN A MASS OF SUBACUTE ABSCESS OF THE CEREBRAL HEMISPHERES, WITHOUT DRAINAGE. C. VINCENT and M. DAVID, Rev. d'oto-neuro-opht. **14**:1 (Jan.) 1936.

A young women was first seen in November 1934 with a syndrome of intracranial hypertension of six weeks' duration. Bilateral ventricular puncture and injection of air in the right ventricle, with subsequent roentgenography, revealed that the left lateral ventricle was not injected and that the right ventricle and the third and fourth ventricles were deviated to the right. A diagnosis of tumor of the left frontal lobe was made. A large frontal flap was raised, and a trocar was inserted at the anterior third of the third frontal convolution. At a depth of 4 cm., resistance was met, which was overcome and an abscess cavity entered, from which 20 cc. of pus was removed. It was decided to close the wound and wait until the condition of the patient improved and the wall of the abscess had become thickened, when the abscess would be removed *en masse*. Decompression and puncture of the abscess brought prompt and marked improvement in the patient's condition. In January 1935 the abscess was dissected out with electrocoagulating forceps; the cerebral cavity was lined with thin muscle fibers and a piece of fascia lata, and the bone flap was replaced. Incisions in the dura and skin were completely sutured, without drainage. The abscess weighed 150 Gm. After operation recovery was uninterrupted. For a few days a marked local reaction occurred, consisting of raising the flap and voluminous edema of the forehead and eyelid, but this was controlled by daily spinal punctures. Union was by primary intention. Eight months later reexamination showed that the patient was in magnificent health.

This is the first instance of complete removal of a subacute abscess of the brain, although several times a chronic abscess with thick walls, which were mistaken for tumor, have been dissected out. This method rests on two principles: First, in the great majority of cases an abscess of the brain is surrounded by a capsule which becomes progressively thicker, and, second, after the first phase of abscess of the brain has passed, the patients are the victims more of intracranial

hypertension than of cerebral infection. The first statement is contrary to the opinion of otologists. The apparent contradiction is due to the fact that at the period when the otologist operates little capsule is present; if a period of from fifteen to twenty days were allowed to pass, the capsule would be present. Thanks to the effects of decompression and puncture of the abscess, one may wait without danger for thickening of the wall to occur. This method has since been applied in seven cases. Only one patient has died, and then not from infection. Vincent and David maintain not that certain abscesses of the brain should not be drained but that drainage should not be instituted indiscriminately in all cases of abscess of the cerebral hemisphere.

DENNIS, San Diego, Calif.

FANTOM MANIFESTATIONS IN A CASE OF LEFT HEMIPLEGIA. ANNE MARIE LOHMANN, Deutsche Ztschr. f. Nervenh. **136**:250 (March) 1935.

Weir Mitchell was the first to call attention to fantom manifestations appearing immediately or soon after amputation of a bodily organ. The sensations projected into the amputated organ usually are of an unpleasant nature. Riese pointed out that the position and color of the fantom organ is frequently governed by the position and color of the organ as it was before amputation took place and that the temperature in the lost organ is felt to be warmer. Adler and Hoff stated that vestibular stimulation, such as freezing with ethyl chloride, has a favorable influence on fantom manifestations. It is uncertain whether such manifestations are due to a central or a peripheral disturbance. Mayer-Gross obtained fantom manifestations in an unamputated arm on stimulation of the plexus. Central paralysis may produce a sensation of enlargement, diminution in size or nonperception on the paralyzed side.

Lohmann reports a case of left hemiplegia in a woman aged 55, with fantom manifestations in the paralyzed side. In 1912, after the patient had had a severe fright due to a sharp thunderbolt, hysterical paralysis of the entire body developed, which left her with weakness of the left side. In 1933 she suffered a slight stroke. In 1934 she suddenly experienced a tingling sensation in the left arm and left leg, which was soon followed by typical spastic hemiplegia on the left side. Speech was indistinct, and mastication was disturbed. Headache, hypesthesia and hypalgesia on the left side and somnolence were present. The blood pressure was 200 systolic and 120 diastolic. A few days after the attack the patient maintained that she could bend her paralyzed fingers and move her left hand, although they still were completely paralyzed. She could see the movements with her eyes closed. These mental manifestations gradually grew in dimension. She soon had the sensation that she could raise the left arm in the air, touch her head with her left hand or keep the left arm in the position of holding a violin, although often she was unable to tell the position of the arm. Similar hallucinations occurred with reference to movement of the left leg. On stretching the right leg, she had a sensation that the left leg was being bent or raised. The patient described the fantom motility in great detail. The manifestations were experienced only in the left extremities. At such times she was under the impression that the limbs were normal and that she had as much strength in the left hand as in the right. At times, in addition to these manifestations, she had a feeling that the left arm was gone. Lohmann notes that psychogenic symptoms were absent during the paralytic period.

The cause of fantom manifestations so far has received no satisfactory explanation. Schilder assigned them to narcissism. The person refuses to concede the lack of unintegrity of his body. Head supported the central theory, on the basis that the fantom disappears when the lesion of the brain embraces the postcentral and the parietal region. Curschmann stressed the physiologic basis, since a strong effort produces symmetrical contralateral movements. The patient described by Lohmann showed such manifestations. She also observed that on stretching the healthy leg she experienced a sensation that the paralyzed leg was being bent at the knee and hip. This represents the position assumed in the act of walking.

BERNIS, Buffalo.

Vegetative and Endocrine Systems

HYPOPHYSEAL INFANTILISM—TREATMENT WITH AN ANTERIOR HYPOPHYSEAL EXTRACT. E. K. SHELTON, L. A. CAVANAUGH and H. M. EVANS, Am. J. Dis. Child. **52**:100 (July) 1936.

The authors present a follow-up study of six cases of hypophysial infantilism reported in 1933 in which four patients were treated with intragluteal injections of an alkaline extract of the anterior lobe of the bovine hypophysis and two were kept as controls. One of the first group died of a cyst of Rathke's pouch, and one showed actual and two apparent stimulation of growth. One of the patients used as a control was treated in the preliminary study with desiccated whole thyroid gland and desiccated whole pituitary gland by mouth and intramuscular injections of a preparation of the anterior lobe of the pituitary gland (not related to the pituitary products under discussion). In the present period of observation this patient received no treatment. During the first period of study the girl grew much less than the average normal child, while in the second period, in which no treatment was given, her growth spurted almost to the average normal increment. The other child demonstrated an increased increment of growth in the preliminary study, when he was receiving the alkaline extract of the anterior lobe of bovine hypophysis, but in the second observation period, during which only thyroid was given, his growth increment practically kept abreast with the normal. On prolonged adminsitration of the extract one patient showed a decreased tolerance to dextrose, which returned to normal within three weeks after cessation of treatment. The extracts used by the authors were contaminated by the presence of the thyrotropic, adrenotropic, sex-maturing and other fractions of the pituitary gland. It was believed that the extracts, while somewhat disappointing in stimulating growth, apparently do not retard maturity and may be useful in the rehabilitation during the growth period of dwarfish persons who are not losing over 50 per cent of the normal growth increment. WAGGONER, Ann Arbor, Mich.

SOME FACTORS INFLUENCING THE LENGTHS OF SURVIVAL FOLLOWING BILATERAL SUPRARENALECTOMY. E. D. SISSON and B. MARCH, Endocrinology **19**:389 (July-Aug.) 1935.

Sisson and March performed bilateral adrenalectomy on sixty-eight rats, divided into six age groups varying from 20 to 70 days, in an attempt to discover factors influencing the period of survival. The length of survival after operation was studied from the standpoints of age, sex, initial body weight and loss of weight after operation. The conclusions suggest that age is the predominant factor, for there is a gradual lengthening of life after operation in direct relation to age throughout the six groups. Females live slightly longer than males. The initial weight apparently bears no relation to survival after operation, while loss of weight is directly correlated with the duration of life. PALMER, Philadelphia.

OBESITY AND OCULAR SYMPTOMS IN MENTALLY ALERT CHILDREN DUE TO HYPOTHYROIDISM. J. P. COSTELLO, Endocrinology **20**:105 (Jan.) 1936.

After a study of a series of patients with hypothyroidism Costello concludes: (1) Hypothyroidism in a growing child does not always affect mentality; (2) obesity is a constant sign of hypothyroidism, and growth is not always affected; (3) myopia or an ocular disturbance is always present, and (4) thyroid substance administered by mouth greatly improves the syndrome but does not completely cure the patient. PALMER, Philadelphia.

CHEMICAL CHANGES IN THE MUSCLE OF THE HYPOPHYSECTOMIZED TOAD. A. D. MARENZI, Endocrinology **20**:184 (March) 1936.

Marenzi studied the chemical changes in the muscles of the hypophysectomized toad. He found that the marked asthenia which develops in totally hypophysec-

tomized toads or in toads in which only the anterior lobe of the hypophysis has been removed was accompanied by modifications in the chemical constitution of skeletal muscle, as shown by its progressively decreased content of glycogen, inorganic phosphorus, phosphocreatine and glutathione and by the reduced production of lactic acid during tetanic excitation. These facts demonstrate that a muscular factor is involved in the asthenia, fatigability and diminished capacity to work shown by the muscle of hypophysectomized toads. Grafts or extracts of either the glandular or the intermedioneural lobe of the hypophysis were found to relieve the condition of asthenia and always to produce an increase in the amount of all the aforementioned chemical constituents, although usually not to the values found in normal animals used as controls.

PALMER, Philadelphia.

THE BIOLOGIC EFFECTS OF PINEAL EXTRACT (HANSON): ACCRUING RETARDATION IN GROWTH AND ACCRUING ACCELERATION IN DEVELOPMENT IN SUCCESSIVE GENERATIONS OF RATS UNDER CONTINUOUS TREATMENT WITH PINEAL EXTRACT. L. G. ROWNTREE, J. H. CLARK, A. STEINBERG and A. M. HANSON, Endocrinology **20**:348 (May) 1936.

Rowntree, Clark, Steinberg and Hanson administered 1 cc. of pineal extract (Hanson) intraperitoneally each day to successive generations of parent rats; the effect on both parents and offspring was noted. They found that administration of this extract tends to increase the frequency of breeding; in the offspring of later generations it decreases the weight at birth and the rate of growth but accelerates the rate of differentiation and development. The effect on the young becomes more marked in succeeding generations. In the second generation, consisting of 138 animals, there was definite retardation in growth, with slight acceleration in sexual development. In the third generation, consisting of 543 rats, there were marked retardation in the rate of growth, marked acceleration in sexual development and slight precocity in bodily development. In the fourth generation, consisting of 155 animals, and in the fifth generation, consisting of 41 animals, there were marked retardation of growth and marked acceleration in the rate of sexual and bodily development. Thus, in the fifth generation the average young rat was less than 50 per cent of the normal weight, was sexually mature in less than half the normal time and evidenced marked precocity from the standpoint of development of the fur, eruption of the teeth and opening of the eyes.

PALMER, Philadelphia.

PRESSOR AND OXYTOCIC FRACTIONS OF POSTERIOR PITUITARY EXTRACT: COMPARATIVE EFFECTS ON BLOOD PRESSURE AND INTESTINAL ACTIVITY. K. I. MELVILLE, J. A. M. A. **106**:102 (Jan. 11) 1936.

Melville shows that the effect on blood pressure and intestinal action of pituitary (posterior lobe) extract, injected intravenously in the unanesthetized dog, varies markedly with the fraction used, even when equal pressor-assayed doses are employed. The presence of the oxytocic hormone may inhibit or abolish the typical effects of the pressor constituent. It is thus concluded that the pressor hormone alone under such conditions causes a fall of blood pressure, stimulation of intestinal activity and defecation, while the oxytocic constituent in sufficient doses exerts a definite antagonistic influence in respect to these actions. These observations may explain some conflicting reports on the clinical usefulness of the agents in question.

EDITOR'S ABSTRACT.

NITROGEN AND SULFUR METABOLISM IN SUPRARENALECTOMIZED RATS. MARTA SANDBERG and DAVID PERLA, J. Biol. Chem. **113**:35, 1936.

Sandberg and Perla studied the nitrogen, sulfur, copper and iron metabolism in adrenalectomized rats. Fecal excretion of nitrogen was unchanged, while that of the urine was increased. Changes in the excretion of urea and creatine accounted

for most of the increase, since ammonia and uric acid were unchanged. The excretion in the urine of total and neutral sulfur was also increased. No change in copper and iron metabolism was observed. These observations are taken to mean that the adrenal glands are associated in some manner with endogenous sulfur metabolism.

PAGE, New York.

THE RELATION OF SERUM PHOSPHATES TO PARATHYROID TETANY. JAMES H. JONES, J. Biol. Chem. **115**:371, 1936.

Jones has shown that the addition of a 4 per cent solution of basic aluminum acetate to diets low in calcium protected rats from the symptoms which usually follow removal of the parathyroid glands. The calcium of the serum remained high and the phosphorus low. This was found to be the case with a diet which did not contain over 0.005 per cent of calcium. If, for any reason, the animals did not eat after the loss of parathyroid function, the phosphorus of the serum increased; the calcium fell, and tetany followed. Apparently, if the phosphorus of the blood can be kept low, the calcium remains above the level of tetany, even though there is a pronounced deficiency of calcium in the diet. If, however, there is a source of available phosphorus, either from the diet or from excessive endogenous metabolism resulting from fasting, the phosphorus of the blood rises, the calcium falls, and tetany appears.

PAGE, New York.

REPORT OF A CASE OF "SIMMOND'S DISEASE," WITH RECOVERY. CHARLES W. DUNN, J. Nerv. & Ment. Dis. **83**:166 (Feb.) 1936.

In 1914 Simmonds described a syndrome of hypophysial cachexia, with the following signs and symptoms: acute onset, rapid loss of weight, sudden amenorrhea, atrophy of the primary and secondary sex organs, hypotension, vertigo, chilliness, a constant sense of coldness of the extremities, cyanosis of the feet and legs, mental and physical asthenia, thickness and dryness of the skin, headache, anorexia and gastric pains. Falta described eleven cases, in four of which autopsy showed destruction of the pituitary gland. Puerperal sepsis, septic emboli, syphilis, cysts and tuberculosis have been ascribed as causes by Riecker and Curtis. The incidence is predominantly high among females.

Dunn presents the history of a girl aged 12, who began to lose weight and had spells of crying, gas pains, vertigo, coldness of the hands, anorexia and amenorrhea. These symptoms were sudden in onset and increased in severity. The blood pressure sank to 74 systolic and 50 diastolic. Laboratory examinations excluded syphilis.

Therapy consisted in the daily injection of 2 cc. of solution of anterior pituitary and weekly injections of 10,000 rat units of estrogen. These were continued for three months, when a consistent gain in weight, rise of blood pressure and onset of the menses occurred. The uterus was increased to about three times the previous size; the breasts enlarged, and the skin became soft. A normal mental state enabled the patient to resume school work. She was receiving at the time of writing biweekly injections of 2 cc. of solution of anterior pituitary and weekly injections of estrogen.

HART, New York.

AN ADRENALIN-LIKE ACTION IN EXTRACTS FROM THE PROSTATIC AND RELATED GLANDS. U. S. VON EULER, J. Physiol. **81**:102 (March 29) 1934.

Von Euler studied extracts of the prostate and other glands of the male genital apparatus. Prostatic extracts from man and the dog, rabbit and guinea-pig showed a pressor action on the circulation of the rabbit. Considerable evidence has proved this action to be derived from a substance closely resembling epinephrine. The hypertensive action was destroyed if the extracts were heated for one hour at 54 C. Other demonstrable effects of intravenous administration of these extracts are: contraction of the urinary bladder and inhibitive action on

the isolated intestine of certain animals. It is suggested that an endocrine function of the prostate is partially proved by the demonstration in comparatively large amounts of a substance probably identical with epinephrine.

PALMER, Philadelphia.

VEGETATIVE NERVOUS SYSTEM IN DEMENTIA PRAECOX. WULF SACHS, South African J. M. Sc. **1**:142 (March) 1936.

Sachs points out that numerous investigations of the vegetative system in psychic disturbances, especially in dementia praecox, have led to contradictory results. One peculiarity of neurovegetative reflexes which leads to special difficulties is the "dissociation" of vegetative symptoms. Sachs mentions "internal dissociation," or the tendency of various organs to differ from one another in their responses to given tests, "group dissociation," or the tendency of various members of a group of drugs to give different or opposite results on a certain organ, and a "general form of dissociation," by which the multiplicity of tests gives rise to difficulty in discovering the true picture of vegetative imbalance.

Sachs studied one hundred Bantu patients with dementia praecox, on each of whom he carried out fifty tests, many of which were repeated. In general he found in a majority of cases irreducible hypotonia of the vegetative system, but the responses were so variable and complex that no constant relationship could be found between the responses and the constitution of the patient. He was consequently unable to draw any conclusions about the value of the various reactions from the standpoint of the pathogenesis, diagnosis and prognosis of the disease. He believes that most of the work of other investigators has been inaccurate because too few cases were studied by too few methods and because observations were poor and tabulations inconsistent. He prefers the psychogenic theory of the origin of dementia praecox but does not exclude the possibility of other, physicogenic factors. He concludes: "It is the psychologic aspect of catatonic behavior which, in my opinion, alone gives meaning to other aspects and which explains the presence of general hypotonia of the neurovegetative system in spite of the muscular rigidity. In paranoid and other forms of dementia praecox, the pattern of the disease is too complicated to enable in each case a relation to be found between mental status and tonus of the vegetative system."

MACKAY, Chicago.

THE ENDOCRINE GLANDS AND THE BRAIN IN OLD AGE. L. EINARSON and H. OKKELS, Ann. d'anat. path. **13**:557 (May) 1936.

A detailed report is given of the autopsy on a woman aged 93, who showed no signs of arteriosclerosis and died of purulent bronchitis. The outstanding features were: a colloid adenoma of the thyroid, hyperplasia of the cortex of the right adrenal gland and extreme atrophy of both ovaries, which were reduced to small masses of connective tissue. The anterior lobe of the hypophysis showed reduction in the total number of glandular cells, with relative increase of the acidophilic cells, proportionate increase in hyaline connective tissue and an increase in colloid. The pineal gland, the parathyroid glands and the pancreas were well preserved.

Only mild pathologic changes were described in the cerebral cortex: scattered senile plaques, cell shadows, pyknotic nuclei and generalized increase in lipofuscin. The neurofibrillary changes of Alzheimer were observed only in the neurons of the lamina ventralis of the cornu ammonis. In the neurons of the inferior olives and in the cerebellar Purkinje cells, the Nissl bodies were replaced by lipofuscin, but otherwise the brain stem and the cerebellum showed no marked changes. The case is compared with a similar one reported in 1912 by Salimbeni and Géry. Here, too, the outstanding features were an atrophic thyroid and a hyperplastic adrenal cortex. The question is discussed whether adenoma of the adrenal gland, with changes in the lipoid (cholesterol) metabolism, might not have some relationship to the absence of atheroma of the arteries and arteriosclerosis of the brain in both cases, which, in turn, prevented senile, degenerative changes of the central nervous system.

WEIL, Chicago.

Cerebrospinal Fluid

THE EFFECT OF INTRAVENOUS INJECTIONS OF SUCROSE SOLUTION (50 PER CENT) ON THE CEREBROSPINAL FLUID PRESSURE, THE BLOOD PRESSURE AND CLINICAL COURSE IN CASES OF CHRONIC HYPERTENSION. FRANCIS D. MURPHY, R. A. HERSCHBERG and ALEX M. KATZ, Am. J. M. Sc. **192**:510 (Oct.) 1936.

The clinical material presented in this paper consisted of: (1) ten cases of benign hypertension in which no constant relationship was shown between high diastolic blood pressure and the spinal fluid pressure, (2) seven cases of malignant hypertension and four cases of chronic glomerular nephritis in which the high diastolic pressure and renal failure seemed to correspond to the elevation of spinal fluid pressure and papilledema. In seven of fourteen cases in which the spinal fluid pressure was 200 mm. of water or above, there was a diastolic pressure of 130 mm. of mercury or above. When from 300 to 500 cc. of a 50 per cent solution of sucrose was injected intravenously, there was prompt and prolonged reduction of spinal fluid pressure, followed by a gradual return to the basic level in from eight to twelve hours. Prompt and profuse diuresis followed the injection; it began about two hours after the injection and continued usually for six hours.

MICHAELS, Boston.

CEREBROSPINAL FLUID IN VASCULAR DISEASES OF THE CENTRAL NERVOUS SYSTEM. E. D. BREWER and C. C. HARE, Bull. Neurol. Inst. New York **5**:5, 1936.

Brewer and Hare report the results of examination of the spinal fluid of 317 patients with various vascular diseases of the central nervous system. 1. Cerebral thrombosis: Of 77 patients with this disease approximately 50 per cent had a normal fluid and 50 per cent an abnormal fluid. The chief deviation was an increase in the total protein content and an increased reaction for globulin. In 3 cases the pressure was abnormally high, and in 7 the cell count ranged from 11 to 143.

2. Cerebral hemorrhage: In 28 patients the condition was diagnosed as intracerebral hemorrhage. The spinal fluid was abnormal in 71 per cent. The chief abnormalities were increased pressure, increase in the total protein content and a positive reaction for globulin. An increased cell count and bloody and yellow fluid were less frequent.

3. Cerebral arteriosclerosis: Specimens of the fluid of 186 patients were examined; 110 were normal in all respects. In 73 patients the fluid showed a positive reaction for globulin; in 68, an increase in the total protein content; in 7, an increase in pressure; in 4, a slight (nondiagnostic) change in the colloidal gold curve, and in 2, an increased cell count.

4. Cerebral aneurysm: In 8 of 11 patients in this group there were symptoms of bleeding, and the fluid showed an increased amount of protein, a positive reaction for globulin, blood or xanthochromia, and increase in the pressure and the cell count.

Brewer and Hare conclude that pleocytosis and xanthochromia may occur in spinal fluid associated with vascular disease as well as with tumor of the brain but that elevation of pressure and, particularly, increase of the total protein content above 100 mg. favor the diagnosis of tumor.

KUBITSCHEK, St. Louis.

THE EFFECT OF INCREASED INTRACRANIAL VENOUS PRESSURE ON THE PRESSURE OF THE CEREBROSPINAL FLUID. T. H. B. BEDFORD, Brain **58**:427, 1935.

Numerous conflicting opinions have been expressed concerning the normal relation of the intracranial venous and the cerebrospinal fluid pressure. Some have concluded that the two pressures are equal (Hill, and Frazier and Peet); others have expressed the belief that the spinal fluid pressure is the greater. Weed and

Hughson (1921 and 1922) concluded that normally the cerebrospinal fluid pressure is always higher than the torcular pressure. This finding was confirmed by Bedford, who found the torcular pressure to be from 25 to 95 mm. of a 4 per cent solution of sodium citrate below that of the cerebrospinal fluid pressure.

That constriction of the veins of the neck is followed by increase in the pressure of the cerebrospinal fluid has been known for some time. Increased production or decreased absorption of cerebrospinal fluid has been offered as an explanation for the change in pressure. Becht found that it is due to an accumulation of venous blood in the cranial cavity and displacement of cerebrospinal fluid into the spinal canal. These observations were confirmed and extended by Weed and his co-workers (1933).

Although the effect on the cerebrospinal fluid pressure of an abrupt and temporary increase in the intracranial venous pressure seems to have been determined with accuracy, little or no work is available on the influence of a prolonged state of raised intracranial venous pressure. It is with this idea in mind that Bedford's experiments were performed. Dogs were used.

The effect of temporary occlusion of the external jugular veins on the pressure of the cerebrospinal fluid and the venous pressure at the torcula was studied. It was found that the cerebrospinal fluid and the torcular pressure attained their maximum heights simultaneously within a few seconds after the veins were occluded. On release of the jugular veins, the pressures returned to their original levels within a few seconds. It was found that after occlusion of the jugular veins the two pressures might rise to nearly the same level. The average proportion of the increase of venous pressure which was reflected in the pressure of the cerebrospinal fluid was 61 per cent.

The effect of prolonged occlusion of the external jugular veins in dogs resulted usually in a fall of the cerebrospinal fluid and torcular venous pressures soon after they attained their maximum height. The cerebrospinal fluid pressure at first falls rapidly and then more gradually, the fall often taking place in a steplike manner. A level approximating the original pressure before the veins were ligated is usually attained after from thirty to forty-five minutes. The pressure then remains steady or continues to fall somewhat below its original level. The fall in the venous pressure is not as rapid or complete. By the time the cerebrospinal fluid pressure has returned to normal, the venous pressure is still several times its normal height, but it drops to normal after some time. Occlusion of the lateral sinuses midway between the torcula and the point at which they are joined by the basal veins resulted in pressure changes similar to those following ligation of the external jugular veins.

The sudden rise of cerebrospinal fluid pressure which follows venous obstruction is generally regarded as due to the direct influence of the raised intracranial venous pressure on the cerebrospinal fluid pressure and not to increased formation of cerebrospinal fluid. Bedford's experiments indicate that a high torcular venous pressure of several hours' duration is not followed by increased formation of cerebrospinal fluid.

Although it is impossible to be certain of the effect of pressure changes at the torcula on the capillary pressure of the choroid plexuses, it is possible that they are closely related. These experiments indicate that the formation of cerebrospinal fluid is not influenced by changes in the venous pressure of the galenic system and favor the view that the process is a true secretion rather than a simple filtration.

As regards the cause of the fall in pressure, it seems probable that the venous pressure falls mainly on account of the development of collateral circulation, and this is responsible indirectly for part of the fall in the pressure of the cerebrospinal fluid. The occurrence, however, of a normal cerebrospinal fluid pressure in the presence of a torcular venous pressure which is several times its original height and the phenomena observed when the external jugular veins are released after obstruction of several hours' duration suggest that there is an actual decrease in the total volume of cerebrospinal fluid.

SALL, Philadelphia.

PHYSIOPATHOLOGIC CHANGES IN INTRACRANIAL PRESSURE ASSOCIATED WITH THE PRODUCTION AND RESORPTION OF CEREBROSPINAL FLUID. RISER, Encéphale **30**:685, 1935.

The experimental and clinical observations which constitute a large part of the data on which this report is based have been collected since 1920. The methods used included simultaneous measurement of the spinal or intracranial pressure and the pressure of the large veins and retinal and systemic arteries, direct examination of meningeal and cortical vessels, as carried out by Donders and Forbes, and perfusion of the brain, either in situ or when isolated. The aneroid manometer of Mainini, which permits readings of positive and negative pressures, was often used.

The main causes of variation in intracranial pressure are the almost complete rigidity of the craniovertebral casing, the incompressibility of the nerve tissue and its envelops, the volume of cerebrospinal fluid and the quantity of blood circulating in the craniovertebral cavity. The effect on intracranial pressure of various liquids injected into the general circulation is explained chiefly by the osmotic tensions of these liquids, in keeping with the work of MacKibben and Weed. The theory of Barré and Klein that only the temperature, not the molecular concentration, of the injected fluid is effective is not accepted. The thermal effects were slight and transitory. Study of the production and resorption of the cerebrospinal fluid is beset with difficulties. Foreign substances introduced into the spinal fluid can be followed into the blood or the lymphatic circulation. These experiments, from which most explanations of the resorption of the spinal fluid have been derived, tell nothing about its destiny. They give information only concerning the evacuation of foreign substances. The one fact which proves the production of spinal fluid is the internal hydrocephalus that results from ventricular block, together with the disappearance of the hydrocephalus when the obstacle is removed. The overproduction of fluid in forced drainage by the Kubie method was confirmed by Riser, Planques and Simovici, but there is no evidence for tissue drainage or for the therapeutic effects claimed. Normal renewal of the spinal fluid seems to exist, but it is slow.

The various hypotheses concerning the site of production and resorption are considered: The theory of Monakow—production by the blood vessels and epithelium of the choroid plexus, diffusion between the ependymal cells and through the parenchyma and absorption by the parenchyma and the meninges—has no evidence in its favor. The theory of Hassin of extraventricular production of spinal fluid and absorption by the choroid plexus cannot be accepted, for it does not explain internal hydrocephalus by mechanical block. The production of spinal fluid by the choroid plexus seems proved, principally by the results of destroying the plexus. The ubiquitous production by the parenchyma and the direct evacuation to the meninges are possible but have not been proved. This mechanism may coexist with production in the plexus. Riser suggests that the plexus may be the essential source, functioning in rapid, episodic production of fluid. The site of absorption remains obscure. The existence of a "one way current," from the ventricles to the meninges, appears certain.

Many facts point to the following conclusions concerning the relation between passive circulatory changes and spinal fluid pressure: Arterial hypertension, constant or paroxysmal, has little effect on the spinal fluid pressure. Venous hypertension, either local or general, always gives rise to hypertension of the spinal fluid. However, the relation between these two factors is not mathematical. Stimulation of the sympathetic nervous system, either directly or by epinephrine and other drugs, produced no change in cerebrospinal pressure, except in so far as there were secondary vagal effects. Stimulation of the vagus nerve resulted in increased pressure, which is explained by the venous hypertension. There is no evidence of any direct effect on the production of fluid or the cerebral circulation. There is no evidence of the existence of an apparatus regulating craniovertebral pressure and cerebral vasomotility in the higher vertebrates. The contractility of the cerebral arteries is limited.

The main factors resulting in pathologic intracranial hypertension are: meningeal lesions with congestion of the choroid plexus and overproduction of spinal fluid, perhaps also with interference with venous absorption in cases of septic meningitis; tumor, in the broadest sense of the word; general or jugular venous hypertension; toxic factors, such as those resulting from renal retention, and mechanical irritation, as in trauma or operation. The action of the last two factors is not clear. Suppuration of the central nervous system, as long as it is distant from the meninges, is peculiarly torpid. Hypertension is slight and always appears late unless the abscess blocks the ventricles mechanically. Chronic aseptic degenerative parenchymatous lesions, such as multiple sclerosis, do not involve any notable evacuation of degenerative products toward the meninges. Their effect on fluid pressure is absent or slight. Acute aseptic degenerative lesions, such as softening, can result in transitory hypertension. Any lesion, whatever its nature, which blocks the evacuation of fluid from the ventricles results in internal hydrocephalus, but the mechanism of communicating hydrocephalus is obscure. The favorable results obtained by Putnam from endoscopic coagulation of the choroid plexus point to hypersecretion of fluid by the plexus.

Hypotension of the cerebrospinal fluid seems to have little or no ill effect when it is permanent, but sudden, episodic hypotension, as in trauma, constitutes a definite syndrome. Thus, Leriche has observed the depression of a cranial scar accompanied by intense headache and an increase in the number of epileptic seizures.

LIBER, New York.

Diagnostic Methods

ELECTROCARDIOGRAPHIC CHANGES DURING ENCEPHALOGRAPHY. MILTON M. ABELES and DANIEL E. SCHNEIDER, Am. J. M. Sc. **190**:673 (Nov.) 1935.

The most frequent electrocardiographic change during encephalography was that due to stimulation of the pacemaker, causing sinus arrhythmia in seven cases, sinus bradycardia in two, phasic sinus slowing in two, sinus tachycardia in three and a combination of these in two. The next most frequent variations were those consequent on migration of the pacemaker (auricular fibrillation). The third most frequent changes were those indicating dominance of the auriculoventricular node or the ventricular foci. There were no appreciable changes in five cases. The majority of the findings are to be attributed to excessive stimulation of the vagus nerve. It is suggested that interference with the conduction mechanism of the heart may play a rôle in death during encephalography, of which a case is cited.

MICHAELS, Boston.

THE EXCLUSION OF NEUROSYPHILIS BY MEANS OF THE HINTON REACTION OF THE BLOOD. J. L. GRUND, Arch. Dermat. & Syph. **32**:569 (Oct.) 1935.

It has been asserted that a negative reaction of the blood to the Hinton test practically excludes the possibility of a positive Wassermann reaction of the spinal fluid and that a patient with a history suggestive of neurosyphilis could be spared the inconvenience of a lumbar punture whenever the reaction to the Hinton test of the blood was negative. This, however, has not been the experience of Grund. He cites five cases in which a strongly positive Wassermann reaction of the spinal fluid, corroborated by definite clinical evidence of tabes, dementia paralytica or cerebrospinal syphilis, was accompanied by a negative reaction to the Hinton test of the blood. Reliance on a negative reaction to the Hinton test as a test for eliminating a diagnosis of syphilis of the central nervous system is therefore unwarranted.

DAVIDSON, Newark, N. J.

SENSE OF SMELL: LOCALIZATION OF TUMORS OF THE FRONTAL LOBE OF THE BRAIN BY QUANTITATIVE OLFACTORY TESTS. C. A. ELSBERG, Bull. Neurol. Inst. New York **4**:535, 1936.

A small extracerebral growth beneath the frontal lobe affects the extracerebral olfactory pathways, while a growth within the lobe affects in part areas within the

brain substance and in part the extracerebral olfactory pathways. Quantitative olfactory tests with the blast and stream injection of odors, previously described by Elsberg, were used in forty-seven cases of verified tumor in or under the frontal lobe. The localization of the growth was made in forty-six instances. Elsberg points out that diminution or loss of smell is frequent in a variety of intracranial lesions, such as postencephalitic states, extensive intracranial hemorrhage or inflammatory lesions, and after severe cranial trauma and that the tests are of value in the localization, but not in the diagnosis, of lesions.

KUBITSCHEK, St. Louis.

OBLITERATING ARTERITIDES: ESTIMATION OF FUNCTION BY MEASUREMENT OF CHRONAXIA. J. MOLDAVER, Encéphale **31**:115, 1936.

Experimentally, Bourguignon showed that local refrigeration produces a chronaximetric syndrome similar to the reaction of degeneration, save that it is reversible. With Laugier he observed that suppression of either the venous or the arterial circulation results in true curarization, with lowering of the chronaxia of the nerve, while that of the muscle remains normal. After circulation is reestablished, the chronaxia of both the nerve and the muscle increases. The muscle contracts slowly when the nerve is excited. This is analogous to reaction of degeneration. All these changes are rapidly reversible. These findings, together with the inadequacy of existing methods, led Moldaver to study the chronaxia in cases of arterial obliteration in the limbs of man. Four cases of intermittent claudication are reported, with figures for the chronaxia of muscles and nerves of the affected parts when at rest, during claudication and after diathermy and the administration of acetylcholine. In all cases oscillometric readings were practically abolished. The chronaxia was increased in all cases, but to different degrees; it responded well to diathermy or the administration of acetylcholine in some cases and poorly in others. The conditions in which the chronaxia was not too elevated and responded to vasodilatation were clinically more favorable than others and corresponded presumably with arterial spasm more than with organic obliteration. Thus, chronaximetry supplies information which oscillometry and other methods alone cannot give.

LIBER, New York.

INVESTIGATIONS OF THE CHOLESTEROL CONTENT OF THE CEREBROSPINAL FLUID. M. BARTH, Arch. f. Psychiat. **105**:191 (July) 1936.

Barth carried out investigations on the cholesterol content of the spinal fluid by means of a new method (Plaut and Rudy) on 387 patients. In a large number of these persons repeated determinations were made, and the results showed the reliability of the method. In normal persons the cholesterol content was usually as high as 0.25 mg. per hundred cubic centimeters, and in only one case did it reach 0.3 mg. Barth agrees with Plaut and Rudy that normally the amount should be no more than about 0.25 mg. and that 0.3 mg. is indicative of a slight rise. The most marked increases were found in cases in which pronounced destruction of the brain tissue had taken place. In cases of tumor of the brain and brain abscess as much as 2.8 mg. per hundred cubic centimeters was shown. In the psychoses (dementia praecox and manic-depressive psychosis) few instances of increased cholesterol were found, and most of these were in cases of chronic deterioration. Barth believes that further investigations should be undertaken, especially since with a method of this type such investigations do not involve practical difficulties.

MALAMUD, Iowa City.

SIGNIFICANCE OF THE SEDIMENTATION RATE IN NEUROLOGY AND PSYCHIATRY. W. EDERLE, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:745 (May) 1935.

A diminished sedimentation time was found in 93 of 270 cases of neurologic and psychiatric diseases studied in the hospital during the course of nine months. A sedimentation rate of 15 mm. during the first hour was considered abnormal.

Seven patients in the series with mental defect showed a normal sedimentation rate; a significantly diminished sedimentation time occurred in 10 (11 per cent) of 97 patients with psychogenic syndromes, in 22 (56 per cent) of 39 patients with organic disease, in 23 (47 per cent) of 49 patients with schizophrenic reactions, in 8 (27 per cent) of 30 persons with cyclothymic reactions, in 2 of 14 epileptic patients and in 16 (73 per cent) of 22 patients with neurosyphilis.

The findings in the psychogenic and neurotic patients suggest that in a certain percentage of cases some form of chronic somatic ailment may be responsible for the symptoms. A decreased sedimentation time is in favor of inflammatory disease. Symptomatic psychoses show more decrease in sedimentation time than schizophrenia. Little change was found in the paranoid form with an insidious onset. The secondary alterations of metabolism, so often seen in states of excitement, probably bear some relation to the sedimentation rate. This altered sedimentation rate may also be a result of somatic changes which precipitated the psychosis in predisposed persons. Motor excitement and impaired nutrition do not of themselves alter the sedimentation rate in the same way. In idiopathic epilepsy no definite change was noted. This fact may perhaps be useful as a means of differentiating this type of convulsive state from symptomatic epilepsy, in which changes in the sedimentation rate are more usual.

Systemic syphilis diagnosed incidentally as the patients were admitted for some other disease showed normal readings. Another group of syphilitic conditions is described with a clinical picture resembling a neurosis—vasomotor instability, recurrent spells of weakness and vague general complaints. In these cases the sedimentation rate was definitely increased. Patients with neurotic complaints who show such a sedimentation reaction should be investigated for syphilis. The spinal fluid in these cases shows some abnormality in the colloidal gold curve and an occasional abnormal protein reaction, but never pleocytosis. In early metasyphilis of the nervous system, including dementia paralytica, the sedimentation rate may be normal or somewhat increased. As the disease progresses, the sedimentation time decreases. This is a manifestation of severe somatic damage, which is present in late stages. The patients are bad risks for malarial therapy. The sedimentation time furnishes a ready clue to the existence of somatic disorders in association with mental reaction patterns.

SAVITSKY, New York.

Encephalography, Ventriculography and Roentgenography

A CASE OF CEREBRAL DEGENERATION WITH ENCEPHALOGRAPHIC STUDY EIGHT YEARS AFTER COMMON CAROTID LIGATION. HERMAN WORTIS, Am. J. M. Sc. **192**:517 (Oct.) 1936.

On Nov. 1, 1926, a trained nurse aged 49 was in an automobile accident, with the only obvious injury a laceration above the left eye. Twelve days later her left eye became discolored and began to protrude slightly. One month later she complained of noises in her head. Sixty-three days after the accident the condition was recognized as one of pulsating exophthalmos, probably due to a traumatic aneurysm of the carotid sinus and cavernous sinus. With the patient under ether anesthesia, ninety days after the accident, the left common carotid artery was ligated, with resulting complete cessation of the bruit, right hemiplegia and total aphasia. The left superior ophthalmic vein was ligated on the one hundred and thirty-third day after the accident. On July 27, 1935, the patient entered the Bellevue Hospital in a disturbed mental state (confusion, disorientation and memory defects). She had shown progressively marked intellectual impairment since the operation, with bouts of amnesia and irritability. Neurologic examination showed that there was 3 mm. of exophthalmos in the left eye, the left pupil was larger than the right and there was poor reaction to light. The left nerve head was pure white. There was right hemiparesis, with most of the accompanying neurologic findings. Encephalograms revealed typical unilateral "hydrocephalus

ex vacuo," characteristic of degeneration of one cerebral hemisphere. The case demonstrates the danger of ligating completely the common carotid artery, without first encouraging the development of collateral circulation by digital compression.

MICHAELS, Boston.

CRANIAL VENOUS SINUSES: CORRELATION BETWEEN SKULL MARKINGS AND ROENTGENOGRAMS OF THE OCCIPITAL BONE. BARNES WOODHALL and ASA E. SEEDS, Arch. Surg. **33**:867 (Nov.) 1936.

A preliminary study of 100 consecutive routine roentgenograms of the occipital bone of normal persons, taken in the anteroposterior projection plane, has demonstrated relative differences and variations in the size of the bony markings of the lateral sinuses that correspond closely to the anatomic observations previously reported. The normal standard of variation, appraised by roentgenographic study, is of clinical value in determining the significance of irregularities obtained by the Queckenstedt test and the dynamics of the venous return from the brain in the presence of thrombosis of the lateral sinus or the jugular vein.

GRANT, Philadelphia.

PNEUMENCEPHALOGRAPHIC DIAGNOSIS OF TUMORS OF THE CORPUS CALLOSUM. C. G. DYKE and L. M. DAVIDOFF, Bull. Neurol. Inst. New York **4**:602, 1936.

Dyke and Davidoff present what they believe is the first description in the literature of the pneumencephalographic appearance of tumors of the corpus callosum. In their series of three thousand air studies, a diagnosis of tumor of the corpus callosum was made or suggested in eight cases. Histories of the patients are presented, with emphasis on the air studies. The characteristic findings produced by tumor of the corpus callosum are: (1) separation and asymmetrical distortion of the lateral ventricles; (2) a sharp defect in the dorsal margin of one or both lateral ventricles; (3) the occasional failure of one ventricle to fill with gas; (4) distortion of the sulci and convolutions on the medial aspect of the brain, and (5) deformity or obliteration of the dorsal and rostral parts of the third ventricle. Conditions which may resemble tumor of the corpus callosum in the encephalogram are: (1) cyst of the cavum septi pellucidi; (2) agenesis of the corpus callosum; (3) intraventricular tumor, and (4) parasagittal tumor.

KUBITSCHEK, St. Louis.

ROENTGENOSCOPIC EXAMINATION OF THE VENTRICULAR CAVITIES WITH IODIZED OIL (ROENTGENIODOVENTRICULOSCOPY). RAMÓN CARRILLO and JUAN ALBERTO AGUIRRE, Arch. argent. de neurol. **14**:77 (March-April) 1936.

In iodoventriculography 4 cc. of iodized poppy-seed oil is injected, but when there is advanced internal hydrocephalus, as much as 8 or 10 cc. is used. Carrillo and Aguirre think that it is possible to follow in the roentgenoscopic plate the displacement of the opaque substance, to establish the form of the ventricles and especially to determine block by means of fluoroscopic examination. Roentgenoscopy at present is only a complement to iodoventriculography. Fluoroscopic visualization of the ventricles with iodized poppy-seed oil produces less distress to the patient than air and permits easy diagnosis of ventricular block.

ALPERS, Philadelphia.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, Feb. 9, 1937

A. A. BRILL, M.D., *President, in the Chair*

UNUSUAL CASE OF INTRACRANIAL ANEURYSM: CLINICAL AND PATHOLOGIC DEMONSTRATION. DR. IRVING J. SANDS, Brooklyn.

History.—M. C., a single woman aged 24, entered the Brooklyn Jewish Hospital on Nov. 29, 1936, at 9:30 a. m., with a history of headache and nonprojectile vomiting for three days. The temperature was 99 F. and the pulse rate from 50 to 60 per minute. One hour before admission she had had generalized convulsions, which were more prominent in the right upper extremity than in the left. There was slight haziness of the left optic disk. The patient was given soluble phenobarbital U. S. P. (sodium phenobarbital) and was removed to the hospital.

Physical Examination.—On admission the patient was semicomatose. The temperature was 100.4 F., the pulse rate 84 and the respiratory rate 20 per minute. There was a port-wine area on the left side of the face. The pupils were fixed, and the left was larger than the right. The fundus of the left eye showed considerable vascular engorgement and slight haziness of the margin of the disk. There was no nuchal rigidity and no Kernig sign. The heart and lungs were not abnormal. The abdominal reflexes were not elicited. All the deep reflexes were present. There was a positive Babinski sign on the right.

Course.—A spinal tap was made immediately on admission, and 3 cc. of a pink fluid was removed; the initial pressure was 170 mm. of water. After this the patient became cyanotic. The pulse became weak, and the rate rose to 150 per minute; the respiratory rate was 10 per minute, and the blood pressure, 108 systolic and 54 diastolic. The stupor deepened. The patient was given epinephrine, caffeine, a 25 per cent solution of pyridine betacarbonic acid diethylamide (coramine) and inhalations of a mixture of carbon dioxide and oxygen. The pulse became imperceptible; respirations ceased at 1:15 a. m., thirty-five minutes after admission. The diagnosis of ruptured aneurysm of the left posterior communicating artery of the circle of Willis was made.

After autopsy had been performed, I learned that the patient had been treated by Dr. Israel Strauss, who forwarded the history.

Past History.—The patient's birth was said to have been normal. As an infant she was noted to have slight flattening of the left side of the face. Later, the teeth on the left were said not to have developed as well as those on the right. In cold weather the left side of the face, particularly the chin, became blue. In 1925, at the age of 13, she had "grip" and was in bed with fever for two or three weeks. Her menses began at about this time; they were usually a week or two late. After the grip-like infection, she had occasional attacks of momentary dizziness and clouded consciousness, with no sensation of falling and no headaches. Sometimes the attacks of confusion persisted for "quite a period." The spells occurred principally when she was out and occasionally at home or at school. Because of the spells, she became worried, nervous and afraid to go out. About a year later she began to see double when looking to the left and sometimes when looking straight ahead. When reading at close range she had no diplopia. At the cinema she sat on the left side of the house, in order to keep her head turned to the right. Her habits were good, and her progress at school was satisfactory.

Roentgenography of the skull in November 1926 revealed nothing abnormal. On July 5, 1927, Dr. Strauss found that she had weakness of the left external rectus muscle but no involvement of the other ocular muscles or of the optic disks. On July 7 he noted also the atrophy of the left side of the face. He concluded that an intracranial lesion was present in the left middle fossa. On November 1928 the patient's general condition was good, but her visual difficulty had become worse during the preceding few months. She now saw two images side by side when she looked to the left, straight ahead or slightly to the right. There was complete paralysis of the left external rectus muscle. In a roentgenogram of the skull taken late in November 1928, Dr. Leopold Jaches discovered irregularity and narrowing of the left sphenoid fissure.

During the next few years the patient was employed as a bookkeeper and stenographer; she had no trouble with her work, although her left eye became practically useless. On April 29, 1931, Dr. Strauss found no change in the optic nerve. The right knee jerk was now more active than the left. In 1933 she noted spots before the eyes, more on the left than on the right. She continued at her employment and had no additional symptoms.

Six weeks before her death she consulted an ophthalmologist for the purpose of having her eyes straightened.

Report of Necropsy.—The dura bulged over the left hemisphere. When it was incised, fluid and clotted blood were noted over the anterior two thirds of the left side of the brain. On removal of the brain a large aneurysm of the left internal carotid artery was observed to have ruptured at its posterior pole. It occupied the inner portion of the left middle fossa. The sphenoid bone was pushed forward to the right. The left temporal lobe was indented by and apparently had adapted itself to the aneurysm. The third and fourth nerves on the left were compressed by the aneurysm. The entire architecture of the base of the brain was distorted, and the central axis assumed an obtuse angle with its apex directed to the right and located at the junction of the cephalic and left borders of the pons. The sixth, fourth and third cranial nerves on the left were much narrower than the corresponding nerves on the right.

Sections of both internal carotid arteries showed splitting of the elastic layer on the left, with loss of the media and replacement with fibrous tissue. Sections from the aneurysm showed replacement of the muscle fibers of the media with fibrous and scar tissue. Section of the brain did not disclose any evidence of old or recent inflammatory changes.

DISCUSSION

DR. ISRAEL STRAUSS: This case is unusual. The patient was 15 years of age when she came to me in 1927. At that time she complained of little except diplopia. A roentgenogram of her skull which had been taken previously revealed nothing abnormal. At that time I found weakness of the left external rectus muscle and atrophy of the face on the same side, which could not be accounted for by a lesion causing weakness of the external rectus muscle. Atrophy of the face had been present apparently for a long time, and I regarded it as congenital, for the mother said that it had always been present. The patient, however, had attacks which seemed to be petit mal. At that time I could not decide on the nature of the pathologic process, and phenobarbital was prescribed. When I saw her on Nov. 16, 1928, there had been no change. Dr. Jaches made another roentgenogram. Here, again, nothing significant was found.

In 1931, when I again saw the patient, there was a slight difference in the knee jerks. Otherwise, there was no change. She made no complaint. The seizures, I think, had ceased. I then changed my opinion and said that I could see no evidence of a neoplasm or an inflammatory process. There had been no progress in the symptoms, and I could not make a diagnosis. Afterward, she consulted Dr. J. M. Wheeler.

I did not see the patient again until May 16, 1936. She had had no headaches and no petit mal seizures. There was no change in the ocular muscles; the

hemiatrophy of the face, of course, was the same. She felt well. She came to ask my advice as to which of two oculists she should go to for operation on the left eye, for cosmetic reasons. She had been told by an oculist that if operation on the muscle were performed the eye could be straightened and the disfigurement of the strabismus lessened. She named two oculists, and I left it to her to make the choice. That was the last I saw or heard of her until Dr. Sands told me she had died of intracranial aneurysm at the Brooklyn Hospital.

This history covers a period from 1927 to 1936, without any progression in the symptomatology. If, for argument's sake it is assumed that I had made a diagnosis of aneurysm, of what good would that have been to the patient? I have diagnosed aneurysm of the internal carotid artery, and surgeons have made exposure. Their attempts to cure the condition have been as futile as my effort to diagnose the aneurysm in this case.

Dr. Emanuel D. Friedman: Was there any history of trigeminal pain in this case? Were there any phenomena of involvement of the temporal lobe at any time? She was a right-handed person, I presume?

I am also interested in the presence of hemiatrophy of the face. It is possible, since the lesion was probably congenital, that the facial atrophy may have been due to a trophic lesion of the ganglion or of the sympathetic filaments which accompany the fifth nerve on that side.

Dr. Irving J. Sands: When I saw the patient, I had none of the history which Dr. Strauss has just reported. I was told only that the patient had a headache, had vomited and had been ill for two days. She had been in good health previously. Diagnosis at that time was relatively simple. Thus far, examination of sections stained for myelin has shown no changes. There has been no evidence of encephalitis. As far as I know, there were no symptoms of trigeminal involvement.

Dr. Israel Strauss: There were no symptoms of involvement of the temporal lobe or of the trigeminal nerve.

Encephalitis Following German Measles. Dr. Charles Davison and Dr. Louis Friedfeld, Brooklyn.

This article will appear in a later issue of the *American Journal of Diseases of Children.*

DISCUSSION

Dr. Armando Ferraro: The valuable contribution of Dr. Davison and Dr. Friedfeld has interest for me more from its clinical than from its pathologic implications. From the clinical standpoint I am particularly interested in cases of infectious disease in which asymptomatic involvement of the central nervous system may result and those in which the involvement may be termed abortive. It is known that in a large number of cases so-called asymptomatic neurosyphilis is recognized because changes are detected in the cerebrospinal fluid. This condition may lead later to severe forms of symptomatic neurosyphilis, such as dementia paralytica. On the other hand, it is known that there is a so-called abortive type of poliomyelitis which would not be diagnosed as such were it not that it occurs in the course of an epidemic of poliomyelitis. The criterion of the epidemic is what makes the diagnosis possible. I wonder, therefore, how often in the course of the infectious diseases of childhood one may encounter either asymptomatic involvement of the central nervous system or an abortive type in which some of the symptoms of change in the central nervous system may be confused with the general manifestations of the disease. Neurologists should train the general practitioner to select from the general picture of these infectious conditions the small signs that point to involvement of the central nervous system, so that these signs may be recorded in the history of the patient.

From the psychiatrist's standpoint, I am particularly concerned with the possibility that in the course of the patient's life psychiatric symptoms may develop the relation of which to the previous infectious condition should always be considered. Asymptomatic or symptomatic involvement of the central nervous system may form the pathologic substratum on which either neurologic or mental symptoms develop, particularly along the line of behavior disorders. It is true that some psychiatrists claim that they can make a clearcut distinction between the behavior disorders following organic disease and those which they consider as part of a functional disturbance. Personally, I believe that there are cases in which such a differentiation is difficult and at times impossible.

Concerning the histologic picture, I think that there is no difficulty in accepting the diagnosis of encephalitis which has been offered by Friedfeld and Davison. The designation seems fully justified. How much this encephalitic process resembles or is identical with that following or accompanying measles I do not know as yet. Here I have failed to observe the demyelinization and excessive proliferation of microglial elements that are characteristic of encephalitis following measles. It is possible that in all these complications there is the same pathologic process, in different stages of development. In some cases there might be a reaction of the tissue to toxins rather than to the infectious agent or virus. This possibility points again to the necessity of studying more carefully the subject of inflammation, in order to find out by examination of accurate experimental and human material whether one can bridge the gap between the histologic picture of the perivascular infiltration common to most infectious diseases and the so-called perivascular proliferation described in most encephalitides following the infectious diseases of childhood.

Dr. E. D. Friedman: This excellent report speaks for itself. I too wish to stress, as Dr. Ferraro has done, the absence of demyelinization in the case in which autopsy was performed. In most cases postexanthematous encephalitis has been accompanied by considerable demyelinization. This raises, as Dr. Ferraro has said, the problem of whether this process is inflammatory with secondary degeneration or degenerative with secondary inflammatory lesions. In the presence of so many excellent neuropathologists, I hesitate to venture an opinion in this field.

I have been connected with the neurologic service of the Bellevue Hospital for nearly twenty years. I used to see there many patients who were admitted because of complications following measles, such as late bronchopneumonia, otitis and mastoiditis, but I seldom saw the neurologic manifestations which have been described, at least not until long after the influenza epidemic made its appearance. In recent years it has not been unusual to meet cases of encephalitis following the exanthems.

This brings up the question of the reason for the appearance of these cases of encephalitis. Do they represent a new disease due to a filtrable virus, or has postxanthematous encephalitis been prseent in the past in latent form? From the immunologic standpoint one might compare the condition in some of these cases with the phenomenon which is occasionally encountered in measles, namely, disappearance of the Pirquet reaction during the height of the measles infection. It seems as though the forces of defense are deployed and engaged in the struggle with the dominant infection. In this way the soil perhaps is prepared for the entrance of this ubiquitous filtrable virus, just as in the influenza epidemic it was prepared for the encephalitis virus. In the absence of any other valid explanation, I offer this as a working hypothesis for the recent increase in the incidence of encephalitis following the exanthems.

Dr. Marcus Neustaedter: What was seen in the basal ganglia and particularly in the substantia nigra in this case?

Dr. Charles Davison: The absence of demyelinization, especially of the perivascular type, in this case should not discourage one, since this is the second instance of meningo-encephalitis following German measles in which histologic study has been made. The other case was reported by Briggs, and the condition was

not studied adequately. He referred to the lesion as a "perivascular infiltration of lymphocytes and polymorphonuclear leukocytes at many points with occasional perivascular red blood cells." If autopsy should be performed in other cases, perivascular areas of demyelinization may be disclosed such as those in a number of the cases of encephalomyelitis following ordinary measles.

The reaction in our case was mostly in the region of the cerebellar peduncles and the cerebellum. Scattered inflammatory foci were observed throughout almost the entire central nervous system, including portions of the basal ganglia. The substantia nigra, however, was free from involvement. Sections were studied from the cortex and the white matter of practically every convolution, as is done in examinations made as a routine. In addition, complete coronal sections through the basal ganglia were also studied. A point to be emphasized was the mild meningeal reaction—hence, the diagnosis meningo-encephalitis.

DEFECTS IN THE VISUAL FIELD OF ONE EYE ONLY IN PATIENTS WITH A LESION OF ONE OPTIC RADIATION. DR. MORRIS B. BENDER (by invitation) and DR. ISRAEL STRAUSS.

This article appeared in the May issue of the *Archives of Ophthalmology*, page 765.

DISCUSSION

DR. JOSEPH H. GLOBUS: The material presented by Dr. Bender and Dr. Strauss is important, for it demonstrates that a certain defect in the visual field may occur early in disease of the brain, affecting only one eye and primarily the temporal portion of the field on the side contralateral to the seat of the tumor. This unilateral and contralateral visual disturbance has been described as a crescentic or hemicrescentic defect. However, some perhaps will disagree with this designation. Perhaps some would class these visual disturbances with the so-called quadrantic defects which have been pointed out by Cushing and others. Nevertheless, it is obvious that some of the defects demonstrated affected mainly the periphery of the visual field and should therefore be recognized as crescentic or hemicrescentic, in contradistinction to the defects commonly known as quadrantic or hemianopic.

Some time ago, from material assembled in the service of Dr. Strauss, Dr. S. M. Silverstone and I studied 171 cases of verified tumor of the brain, with the idea of correlating the anatomic lesions of the brain with the carefully studied defects in the visual fields. We also came to the conclusion that the early manifestation of damage of visual fibers by a tumor, and probably by other lesions, is involvement of the visual field on the side opposite the site of the tumor. The cases in which early defects in the visual fields could be studied and recognized were few. In a group of 171 cases we found only 1 instance in which a unilateral quadrantic defect was observed on the contralateral side. Bender and Strauss were more fortunate in assembling a larger number of such cases. It is also significant that in only 49 of the 171 cases were visual field defects presented which could be considered as reliable and useful for our studies. In these 49 cases we detected one constant finding: The defect in the visual field on the side opposite the lesion was always larger than that on the ipsilateral side. That, in itself, supports the observation that the earliest manifestation of involvement of the visual field is on the contralateral side.

The explanation for this we were not able to determine, even by careful study of the material. The reason is that one cannot exclude many factors which are introduced by surgical intervention, such as the destruction of tissue and secondary edema which take place in the terminal days of the patient's life. Some day we hope to study this more carefully, and then perhaps we shall find an explanation for this condition.

I wish to call attention to other observations we have made on our material which have bearing on this discussion. Cases of tumor of the parietal lobe have been described in which quadrantic defects were shown. Curiously, in our material we observed that when hemianopic defects occurred in association with tumor of

the parietal lobe the neoplasm was usually encapsulated. An infiltrating tumor is less likely to cause quadrantic or hemianopic defects. Another observation is that as the site of a tumor shifts backward toward the calcarine area, along the fibers of the optic radiation, the quadrantic defect is less common, and a complete hemianopic defect is more likely. This was true in our material and is shown also in the findings reported by Dr. Bender and Dr. Strauss. On the other hand, the more anterior the seat of the tumor, which may reach about the middle of the temporal lobe, near the level of the turn of Meyer's loop, the smaller the defect in the visual fields assuming the so-called quadrantic outline. Moreover, my findings are not out of accord with the observation that a unilateral defect in the visual field is a condition which one is likely to overlook and to ascribe to a noncerebral disease.

Dr. Israel Strauss: As Dr. Globus stated, most of the cases which we have described occurred in the service subsequent to the exhaustive analysis of field defects which he and Dr. Silverstone published. We are not trying to disprove the importance of the quadrantic defect, as pointed out by Cushing. We are showing that with careful perimetry one may find extremely early a crescentic defect, which is antecedent to the later quadrantic defect so well described by Cushing. This provides a method for early diagnosis of the presence of a tumor and its location, with the reservation pointed out by Dr. Globus. I may add that in case 10 Dr. Bender showed not only the gradual development from a temporal quadrantic defect to complete hemianopia but the recession. I saw the patient recently. She is well except for slight residual motor aphasia; so I am convinced that the diagnosis of encephalitis at the time of her discharge was correct and that there is no possibility of tumor. This is the only case in our series in which a tumor was not the etiologic factor. Evidently, an inflammatory lesion may occasionally produce a picture such as we have shown, progressing to complete hemianopia, with restoration to the normal.

A Study of 50 Cases of Bromide Psychosis. Dr. Frank J. Curran.

Although bromide psychosis has been known since 1869, no attempt, to my knowledge, has been made to restrict the indiscriminate sale of bromides to the laity. Since Wuth's contribution in 1927 (Rational Bromide Treatment: New Methods for Its Control, *J. A. M. A.* **88**:2013 [June 25] 1927) an accurate method of determining the presence of bromides in the blood is available. Bromides replace chlorides in the blood, and toxic symptoms may be expected when from 25 to 35 per cent of the total halogen content is replaced by bromides, i. e., when the bromide concentration of the blood is over 150 mg. per hundred cubic centimeters; replacement of 40 per cent is usually considered fatal. In several hospitals for psychopathic conditions at least 2 per cent of all patients admitted had mental symptoms due to or increased by bromides, while from 7 to 40 per cent showed bromides in the blood. Epileptic patients appear to have a greater tolerance for bromides and to require a much higher bromide concentration in the blood to cause the development of toxic or psychotic symptoms.

The chief symptoms of bromide intoxication are mental torpor, acne, coated tongue, emaciation, digestive disorders, impotence or menstrual disturbances, sluggish pupillary reactions, slurred speech, unsteady gait, tremors of the tongue and fingers and changes in reflexes (hyperactivity, sluggishness or absence of deep reflexes and absence of superficial reflexes), usually without pathologic reflexes.

The most common type of bromide psychosis is delirium, which is usually of from three to six weeks' duration. Cases of bromide hallucinosis, although rare, have been reported. The Korsakoff syndrome is not infrequent. The acneform rash occurs only occasionally in cases of bromide psychosis; one observer found it in only 4 per cent. Fatalities in as high as 11.7 per cent of cases have been reported.

A report is given of 50 cases of bromide psychosis at the Bellevue Psychiatric Hospital. Seventy per cent of the patients were women. Thirty-three patients had a delirious reaction, in which the outstanding diagnostic symptoms were: paraphasic disturbances in speech, visual hallucinations "at a distance," confabulatory defects in memory, vestibular disturbances with ideas pertaining to boats and nets, ideas dealing with electricity and occasional findings of micrographia, micropsia and macropsia.

A few cases are described in detail, including one of bromide hallucinosis. Up to the present, only 5 or 6 cases of a similar condition have been reported. A detailed report is also given of the case of a woman who had had an obsessive neurosis of ten years' duration; after bromide delirium she has been free from mental symptoms for the past seventeen months. The experimental production of bromide intoxication or delirium in cases of melancholia and schizophrenia is discussed.

The majority of the patients in this series used bromides after alcoholism. In some patients the bromide psychosis was superimposed on other mental diseases, including schizophrenia, manic-depressive psychosis and psychosis with cerebral arteriosclerosis.

Treatment of the intoxication or psychosis consists of stopping the use of the drug, giving sodium chloride by mouth or by intravenous injection, forcing fluids and controlling the stage of excitement with wet packs or continuous baths.

In conclusion, it should be emphasized that bromides are eliminated slowly, that they accumulate rapidly even in doses of from 45 to 60 grains (2.9 to 3.9 Gm.) daily and that delirium may occur within a few weeks, even from ordinary therapeutic doses. Now that restrictions on the sale of barbiturates and chloral hydrate are being made in some sections of the country, the laity will resort even more frequently to the use of bromides. Appropriate legislation should be secured to curb the indiscriminate sale of bromides to the public.

DISCUSSION

DR. LELAND E. HINSIE: Dr. Curran had to condense his paper considerably and therefore was unable to give one of the most important features, at least to me, of his communication—an excellent delineation of the so-called intoxication syndrome. I would rather look on the reaction as an intoxication syndrome than as bromide psychosis. I believe that beneath the clinical syndrome produced by the drug there is, as Dr. Curran has indicated, a more fundamental difficulty; for, as he pointed out, the vast majority of the patients exhibiting this intoxication syndrome presented other psychotic disorders when the features of intoxication were terminated. Most of them exhibited alcoholic psychosis, as in 48 per cent of the cases, schizophrenia or cerebral arteriosclerosis. At any rate, the important features behind the intoxication syndrome were deeply lying factors, fundamental to the life of the patient.

It seems to me that before Dr. Curran puts himself on record as having described a bromide psychosis, it would be desirable to study a series of patients as a control, to find out whether the same syndrome might not be exhibited when other drugs are employed. It would be an interesting, but difficult, procedure to find out how much personality difficulties permeate the syndrome which Dr. Curran calls the bromide psychosis. I do not intend to elaborate on that further.

SIGMUND FREUD AS A NEUROLOGIST. DR. SMITH ELY JELLIFFE.

Practically no literature in English contains any summary of the earlier work on neurology by Freud. The twelve volumes of his "Collected Works" contain none of these studies, and practically no writer who has considered Freud's works has any knowledge of an important part of his early training. Even his autobiography speaks only modestly of a "few articles." Parts of the present paper were prepared last May in the hope that they might be presented to the American Neurological Association in commemoration of Freud's eightieth birthday; only a

disjointed presentation is offered here, by reason of restrictions in time. Reference is made to the early work in Brücke's laboratory, when Freud was only 20 years of age, and to notes on his friends there, Exner and von Fleischl and the nature and quality of the work and workers in Brücke's laboratory at the time. Brücke was a pupil of Johannes Müller, and hence concepts of specific energy were current. Stricker, the histologist, and others were all ardent evolutionists, and Freud himself was deep in Goethe and Darwin. Brücke put him to work on a problem of phylogenetic significance, namely, the giant nerve cells of Ammocœtes, and Freud wrote two illustrated papers on this topic. He also worked with Claus at the zoologic station on a problem in comparative histology. Other papers which he produced during the six years he was in Brücke's laboratory are cited briefly. His disappointment at being denied an academic career threw him into the practice of medicine, and he continued his anatomic studies, now on human subjects, in Meynert's laboratory, working at the same table with Bernard Sachs and M. Allen Starr, of New York (from 1882 to 1884). He went to Paris in 1885 and worked with Charcot, translating his lectures. With Darkshevich he wrote a paper on the acoustic nucleus and the interolivary body. Other papers on anatomy were written before and after this period. Two of them were abstracted at length by Dr. Starr in the *Journal of Nervous and Mental Disease.*

Freud's autobiography tells the story of his interest in cocaine and the coca plant. The present paper gives details of two or three papers on this subject.

Clinical papers on syringomyelic dissociation, basilar symptoms in a case of scorbutus, localized with great accuracy in the best of the Meynert tradition, multiple neuritis, etc., are referred to. Also, Freud's work at the Kassowitz Institute on cerebral diplegias and the large monograph on the general subject of this condition contributed to the Nothnagel system; these belong to the period in which Freud was turning more and more to study of the psychoneuroses. Freud's paper on aphasia never received the attention it deserved. Although it upheld the thought of Hughlings Jackson, the English, strangely, do not mention it. Even Head does not cite this study in his bibliography. Goldstein, in his paper published in 1910, gave proper credit to Freud's work on aphasia. The present paper ends with the closing sentence from a recent article by Brun, of Zurich (*Schweiz. Arch. f. Neurol. u. Psychiat.* **37**:200, 1936), which deals with the same material in more condensed form. The appraisal follows:

Looking back again over the neurologic work of Freud, one recognizes distinctly a clear guiding line in the progress of his studies. Freud started, as it were, from the ranks, as a private; yet from the beginning he carried the commander's staff in his knapsack. From his first investigations on the structure of the spinal ganglia and the spinal cord of the most primitive vertebrates, his observations on the finer structure of the elements of the nervous system and his anatomic studies on the brain, he advanced gradually to recognition of the most complicated clinical disturbances. Not until then did he venture on the complex problems of brain pathology, such as the teachings on aphasia, passing at the very last to investigation of the functional neuroses. His thorough anatomic and clinical neurologic training served as a guarantee that in tackling this last and most difficult problem he would remain on a solid biologic basis and would not, therefore, be led too far astray. Thus, the unprejudiced critic, in an evaluation of the results of psychoanalytic investigation, will remember the long and tedious road which Freud has traveled and, before rejecting any of them, will admit modestly that the later findings of the eminent neurobiologist in the domain of the pathology of neurosis presumably are not less solidly founded, at least, than the results of his neuropathologic investigations in the early period of his scientific studies.

DISCUSSION

DR. A. A. BRILL: I was pleased to hear Dr. Jelliffe present this paper, for many persons imagine that Freud started as a psychoanalyst, without any neurologic or psychiatric background. I have always spoken of Freud's early works as an argument against those who believe in psychoanalysis, as such, without a psychiatric background.

When Dr. Jelliffe wrote me that he wished to read this paper here, he told me that Dr. Bernard Sachs would discuss it. He thought naturally of Dr. Sachs, because Dr. Sachs worked with Freud when he was a budding neurologist. However, it flashed through my mind that in selecting Dr. Sachs, Dr. Jelliffe may have unconsciously wished to gratify a revenge fantasy. For since 1908, when I started to speak here of Freud and his psychoanalytic discoveries, in which I was soon joined by Dr. Jelliffe, Dr. Sachs has always been our nemesis. He has ever been the consistent critic of Freud's theories. What could he have said after hearing this masterly presentation by Dr. Jelliffe? Dr. Sachs, being a just man, would have said that Freud is a great neurologist in spite of everything. However, unfortunately Dr. Sachs had to leave town, so that he cannot be here this evening. Some psychoanalysts, as you know, do not believe in accidents! Dr. Jelliffe then conceived the happy thought of asking a man who, although he has not worked with Freud, is nevertheless thoroughly versed not only in neurology and psychiatry but in the works of Freud. I take great pleasure in presenting Dr. Kurt Goldstein, who will discuss this paper in place of Dr. Sachs.

DR. KURT GOLDSTEIN: All will be grateful to Dr. Jelliffe for his excellent review of the early scientific work of Sigmund Freud. Not only most neurologists but many psychoanalysts are unaware that Sigmund Freud made many important contributions concerning the anatomy, physiology and organic diseases of the nervous system. It may be that some of these studies are better known to neurologists than to the analysts who have, so to speak, suppressed, consciously or unconsciously, this part of their master's work to such a degree that they did not even include it in his collected works. This negligence would perhaps be understandable if the early papers were only accidental products of a genius in development—especially if they were in opposition to, or at least had no inner connection with, his essential work, which is of such overwhelming importance in a consideration of psychoanalysis.

This explanation may be valid for some of Freud's early pamphlets, but it does not hold for others. If it is true that the topics differ essentially from the interest of psychoanalysis, the attitude which determines the choice of topics and their elaboration must claim great interest not only for general medicine, psychiatry and neurology but for analysis. Some of these papers contain *in nuce* many of the ideas which became important in psychoanalysis.

In his first investigations, which are concerned with comparative anatomy, there appears the biologic-genetic attitude which Freud's thinking should never give up. This attitude was developed later, especially under the influence of the ideas of Hughlings Jackson, in Freud's paper "Zur Auffassung der Aphasien" (Leipzig, F. Deuticke, 1891).

I wish to remark especially concerning this work on aphasia, which, in spite of its usual neglect by researchers in aphasia, has great historic importance in the development of the concept of speech disturbances, as I have stressed since my first investigation in this field. It points to the foresight of the young Freud that, at a time in which the ideas of Jackson were considered strange and his procedure was thought to be wrong, he was one of the few who recognized the immense importance of this greatest neurologist of his time.

Under the influence of Hughlings Jackson, the functional type of consideration came to the foreground in the thinking of Freud, in opposition to the anatomic, localizing point of view, or, better, he attempted to separate the phenomena which are to be understood on the basis of localization from those which are to be explained only functionally. Thus, Freud, in his paper on aphasia, separated the localized periphery as the place of projection from its central representation, for which real localization is impossible. In the higher parts of the nervous system there is representation not in the topographic, but only in a functional fashion. Thus, Freud was one of the first authors who—in opposition to the ideas of famous neurologists like Meynert, Wernicke, Lichtheim and others, which were then much in vogue—dared to deny the localization of images of language within circumscribed centers and tried to understand the complexities of aphasia on a

basis much closer to concepts of a very modern kind, which have been supported by facts only in the last decade. Disturbances in speech are, for Freud, not defects in single performances but expressions of disintegration of function. Freud arrived at this assumption not only through the ideas of Jackson and Bastian but from his own analysis of the relationship between the organic lesion and the disturbance. An organic lesion does not totally disturb some parts of the nervous system and preserve others but usually represents functional disintegration. The apparatus reacts as a whole to the existing lesion. To the functional disintegration the symptoms correspond. Freud has drawn from this result a consequence which has been important for psychoanalysis: This functional change may also be produced by nonmaterial damage.

This disintegration does not change all performances in the same way and does not lead to accidental selection between preserved and damaged performances. He stressed the great importance of early acquired performances and their influence on the performances of later life and the configurational aspect of the symptomatology which arises in the individual person. This thought returns in the basic concept of psychoanalysis.

Speech is, for him, a uniform phenomenon, and all defects in speech are disturbed in this complex system of association which the speech region represents. This unification is in close relationship to the assumption that all performances and their disturbances are to be understood only in accordance with the personality to which they belong—an idea which also had its creation in Jackson but towards which Freud inclined. This point of view should become important for Freud's consideration of neurotic symptoms as expressions of a changed personality. I think it is one of the greatest merits of Freud that, at a time when psychology and psychopathology believed in the possibility of dissolving all phenomena into isolated parts, a more or less mechanical synthesis of which should represent psychic life, he pushed the factor of personality into the foreground. It was a great merit in Freud, even if he almost obscured this point of view by stressing so extremely the drives in the characterization of personality.

Freud advocated in his paper on aphasia the concept of a psychosomatic parallelism. He tried to find an understanding of neurosis from the same point of view. A drive was for Freud, at the beginning, the whole of not only the psychic but the chemical and psychic events. But the fight against the extreme somatic consideration of disease prevalent at that time brought him to an overestimation of the psychic moment which could be maintained, in view of the facts, only by the construction of the unconscious. However, this excellent observer of facts was forced to see that some phenomena are not to be understood in this way, and he then went over to somatic explanations of symptoms; thus, the somatic moment again burst forth, so as to say, in his theory of anxiety, in his paper entitled "Beyond the Pleasure Principle" and so on. This change in the point of view, which makes some of his papers so difficult to read, is not accidental but was determined by his acknowledgment of the ruling theory of the psychosomatic parallelism on which he based his explanations of speech disturbances but which is, indeed, an adequate theory for understanding facts of life.

I am not able to explain that concept here (Psychoanalyse und Biologie, 1927). I wish to stress that, in my opinion, this inadequacy is due to lack of conformity in the theories of modern physiology as well as of psychoanalysis. Even a genius is a child of his time. If I see it correctly, it was the fate of Freud not to achieve the goal of understanding human behavior at its very depths, to which he was closer than any one else, because of his prepossession with certain scientific prejudices of natural science of his time. Psychoanalysis, in spite of its revolving opposition to ruling ideas, is to be understood only from the scientific background of the late nineteenth century. It is particularly thrilling to study the early scientific work of Freud, because it gives an illuminating insight into the creative originality of Freud, as well as the source of some essential failures and restrictions of psychoanalysis.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, March 18, 1937

FRANCIS J. GERTY, M.D., *President, in the Chair*

HYPEROSTOSIS FRONTALIS INTERNA; DEGENERATIVE DISEASE OF THE BRAIN. DR. NORMAN REIDER, Topeka, Kan. (by invitation).

CASE 1.—A woman aged 52, whose previous history was without significance except that she had undergone hysterectomy at the age of 33 for the relief of a fibroid tumor, became nervous, lost weight and began to have difficulty in finding words. Two years later she had lost orientation for time, though orientation for place and person remained good. She had severe headaches behind the left eye and became gradually worse, being unable to understand what she read or to write even her name.

Examination revealed ocular proptosis and a positive von Graefe sign but no tenderness of the skull. The only neurologic findings were the aphasic manifestations. She was somewhat distressed by her difficulties of expression but, for the most part, was pleasant, and even euphoric. Laboratory studies revealed nothing significant. An encephalogram revealed only mild hydrocephalus. Roentgenograms showed a round, uneven shadow in the frontal region, which in some views appeared to be trabeculated.

The clinical diagnosis was Alzheimer's disease. The condition progressed to complete helplessness, and the patient died about three months after examination.

Postmortem examination revealed hyperostoses of the calvarium in the frontal and temporal regions on the left. The left frontal lobe was smaller than the right because of pressure from the hyperostoses. Microscopic study revealed the neurofibrillar and vascular changes with numerous senile plaques characteristic of Alzheimer's disease.

Case 2.—A woman aged 40 had had menstrual irregularity since puberty, at the age of 11. When 26 she suffered a severe cranial trauma, with unconsciousness for several weeks. She married at the age of 28 and had two miscarriages and one tubal pregnancy. At the age of 37 she became fatigued and several months later began to have numerous attacks of petit mal. When 39 she showed poor memory for recent events. Hyperostoses in the frontal region were detected, and amino-acetic acid was prescribed.

Physical and laboratory examinations revealed no pathologic changes other than the loss of memory. An encephalogram revealed mild cortical atrophy.

Comment.—The association of frontal hyperostosis with degenerative disease of the brain is worthy of report, but no conclusion can be reached other than that there seems to be a definite, though obscure, relationship between the craniopathy and the neuropsychiatric and endocrinopathic symptoms.

DISCUSSION

DR. HAROLD C. VORIS: Will Dr. Reider state how much spinal fluid was removed at encephalography?

DR. NORMAN REIDER: In the first case 95 cc. of fluid was removed, and in the second, 100 cc. Withdrawal was continued until sufficient evidence was secured of what was sought; it was then stopped. In each case a great deal more fluid could have been withdrawn.

MYELOMALACIA WITHOUT THROMBOSIS FOLLOWING INDIRECT TRAUMA (STRAIN). DR. LEO STONE and DR. HARRY N. ROBACK, Topeka, Kan. (by invitation).

This article was published in *The Journal of the American Medical Association*, May 15, 1937, p. 1698.

DISCUSSION

DR. PETER BASSOE: This is an interesting contribution to a difficult subject. I shall mention briefly the case of a patient seen by Dr. Lewis Pollock and myself, a youth aged about 19, who had a vague injury, a carbuncle on the back and, later, a syndrome suggestive of syringomyelia or intramedullary tumor, with a great deal of sensory disturbance. When I saw this patient a few months later, he presented a syndrome more like multiple sclerosis, with the sensory symptoms almost absent.

Some time afterward he was seen by Dr. Temple Fay, of Philadelphia, who made a diagnosis of "thrombophlebitis of the meningorachidian veins." Fay said that he had seen 5 cases of this type and would report them before the American Neurological Association this year. If he has made a report of any cases previously, I have not seen it. He emphasized the two features in this case—the history of comparatively slight injury some time before and subsequent infection, which in his cases has been streptococcic. Dr. Roback said there was no thrombosis in the case which he and Dr. Stone reported, and I assume that that examination included the meningeal and spinal veins.

DR. ROY R. GRINKER: It is extremely difficult to draw conclusions from examination of a specimen ten months after the onset of the lesion. Infectious processes arising after mild trauma, actual thromboses of blood vessels and hemorrhage due to rupture of central vessels, as well as the direct effect of trauma to the spinal cord, may produce this syndrome of the central gray matter. The pathologic changes may be identical, no matter what the cause. Hence, I believe this paper does not add to etiologic considerations of central lesions in the upper portion of the spinal cord.

DR. HARRY N. ROBACK: When I studied the cord in this case, I was perplexed as to the pathogenesis, and I am still uncertain about it. I did not perform the autopsy. I probably should not have thought of dissecting the arteries back to the aorta and the subclavian branches. If I should encounter a similar case, however, I shall surely do so. I think that this procedure is extremely important, especially in view of what Winkelmann has said—that thrombosis need not appear in the cord but that it may occur at the origin of the lateral spinal arteries from the aorta. That is worth proving, for it might help to settle questions concerning the pathogenesis of myelomalacia following physical strain.

ELECTRO-ENCEPHALOGRAPHY IN THE DIAGNOSIS AND LOCALIZATION OF INTRACRANIAL LESIONS. THEODORE J. CASE (by invitation).

The diagnosis of epilepsy is greatly aided in cases of doubtful character in which one fails to see an attack or in which a suspicious history is given by the presence in the electro-encephalogram of any of the following features: the frank seizure pattern; an abortive seizure; a subliminal seizure of low voltage; peculiar waves resembling an attack but without the characteristic features, such as the spike; a wave with a rhythm of 3 per second, identical with the frequency in the minor attack, which appears when the eyes are closed, or various rhythms which are even multiples or submultiples of the frequency of waves in the attack.

In examination of 5 children, 9 or 10 years of age, all of whom were subject to frequent petit mal attacks, 4 were found on closing the eyes to show a wave with a frequency essentially identical with that of the seizure, that is, about 3 per second. This observation was repeated several times on each subject and on one patient on two different days. The appearance of this 3 per second rhythm was not associated with any obvious clinical evidence of an attack and, like the alpha rhythm, it came and went in spindles for long periods while the eyes remained closed. The fifth child on closing the eyes showed only the normal 10 per second rhythm, without evidence of a 3 per second wave.

The position of an intracranial lesion is indicated by electro-encephalography, first, in the localized presence of unusual rhythms and, second, in certain epileptic phenomena.

A woman aged 20 who since the age of 13 had had episodes of peculiar sensation in her left leg, making it necessary to stop walking and rub the leg, had in the year following the onset of these feelings of numbness experienced minor attacks, which were preceded by numbness in the left leg. In the last two years these phenomena had involved the left hand also. Lately she had had major seizures.

Electro-encephalography revealed a wave sharply confined to the region over the right frontal lobe, which had a frequency of 92 cycles per second and an average amplitude of from about 60 to 100 microvolts and which was almost continuous except for a degree of waxing and waning for the duration of the record —a matter of perhaps an hour.

A man had an osteoma of the right frontal sinus invading the anterior cranial fossa to a slight extent, which was not considered sufficient, however, to account for the epileptic attacks which he had had for two years, with predominance on the left side, nor for the weakness of the left side of the face, changes in reflexes and Babinski sign which he showed on examination.

An electro-encephalogram showed, besides large, slow waves localized to the right frontal region, localized epileptic attacks having the form of minor seizures but of much greater duration and very small voltage—about 40 microvolts. These attacks were without clinical evidence of any disturbance, and during and after them the patient denied having any realization that anything unusual was happening.

At operation rather dense arachnoid adhesions were seen involving the right frontal lobe as far back as could be explored. Thus, the presence of a pathologic basis for the localized alteration in the records of the brain potentials could be verified.

DISCUSSION

DR. EDWIN M. MIKKELSEN: How is the patient attached to the apparatus?

DR. PETER BASSOE: The subject is interesting, but I was particularly intrigued by the tracings that showed oscillations without any one being aware of an attack going on. I wish to know something more about this. It may explain some of the mental changes that epileptic patients may undergo, even when manifest attacks are few.

DR. THEODORE J. CASE: Various methods of placing the leads are employed in different laboratories. The method my colleagues and I have used employs three amplifying channels grounded at a common point, which is usually placed at the vertex of the head, while the three input leads of the amplifier are placed separately over any regions in which one is interested. We usually place one lead over each frontal region and one over the occipital area. The channel in question will then record the voltage between the vertex and its respective electrode on the frontal or the occipital region, as the case may be.

There are, besides the subliminal seizures that have been pointed out, various abortive seizures and other waves which are difficult to interpret but which also occur without the patient presenting any clinical manifestations. These, I believe, are real manifestations of epilepsy. Just how far these conditions must go in order to cause clinical symptoms I do not know. Apparently, in an attack there has to be a frequency of at least 3 or 4 oscillations a second before the patient will show clinical evidence and one can see that the patient has an attack by looking at him. Most of the children bat their eyes a little or stare; that is about all they do. Most of them show a frequency of about 20 oscillations in an attack. I should fancy that there would have to be a frequency of about 4 oscillations and probably a voltage of at least 80 microvolts before clinical manifestations could be observed.

SECONDARY VESTIBULAR FIBERS AND THE MEDIAL LONGITUDINAL BUNDLE. DR. A. R. BUCHANAN (by invitation).

Lesions were produced in the vestibular nuclei of a large number of cats, using a Horsley-Clarke stereotaxic instrument. The animals were killed from eleven to

fifteen days after the operative procedure, and the brains and spinal cords were removed and fixed according to the modified Marchi technic recommended by Swank.

The course of the secondary vestibular fibers, as determined by the resultant degeneration, is as follows: Axons of cells in the medial vestibular nucleus course caudad and rostrad in the contralateral and homolateral medial longitudinal bundles; Deiters' nucleus gives rise to fibers which proceed rostrad in the contralateral medial longitudinal bundle and in the extreme lateral horn of the homolateral bundle (ascending tract of Deiters); other axons from Deiters' nucleus descend in both medial longitudinal bundles and in the homolateral vestibulospinal tract; Bechterew's nucleus contributes fibers to the homolateral ascending medial longitudinal bundle and to the homolateral vestibulospinal tract; the descending vestibular nucleus gives origin to fibers which descend in the medial longitudinal bundle of both sides.

Ascending fibers from the medial nucleus terminate chiefly in the nuclei of the oculomotor nerve on the contralateral side, while the descending fibers from the same nucleus terminate in the anterior gray columns of the cervical and thoracic portions of the spinal cord. Axons of the cells of Deiters' nucleus terminate in relation to the abducens nucleus of both sides and in the oculomotor and trochlear nuclei of the opposite side; descending fibers from this nucleus end in relation to cells of the anterior gray column at cervical levels on the contralateral side and in relation to the same cells throughout the length of the spinal cord on the homolateral side. Fibers from Bechterew's nucleus terminate in the trochlear and oculomotor nuclei of the same side and, by way of the homolateral vestibulospinal tract, in relation to cells of the anterior gray column in the cord. The descending nucleus distributes fibers to the cells of the anterior gray column of both sides at the cervical levels of the cord.

PHILADELPHIA NEUROLOGICAL SOCIETY

Dinner Meeting, Feb. 26, 1937

FREDERIC H. LEAVITT, M.D., *President, in the Chair*

PRESIDENT'S ADDRESS: "IT IS TO LAUGH." DR. FREDERIC H. LEAVITT, Assistant Professor of Neurology, the University of Pennsylvania Graduate School of Medicine.

It is said that all the world loves a smile, and most of it enjoys a laugh. It is natural, therefore, that one should become curious about those delightful little human assets, perhaps the more as one observes their manifestations in the ordinary experiences of every day life among the healthy and the diseased. The question "What does laughter mean?" has intrigued many minds and has led to much conjecture and the formulation of many theories. What can a study of this reaction teach as to evolutionary unfolding and the curious "things" called emotions, and how may this knowledge be utilized to aid in diagnosing and relieving some disease conditions?

The Bard of Avon wrote in the "Comedy of Errors," "No longer will I be a fool, to put the finger in the eye and weep, whilst man and master laugh my woes to scorn," and, in a contrasting mood, in "Coriolanus," "'Tis as fond to wail, as 'tis to laugh." Immortal Shakespeare thus contrasted utilization of this much employed word. Why should neuropsychiatrists be interested in the term? Surely, it is one that is used full much in this day and age. One believes the laugh to be a natural heritage from evolution's flower—a last gift perhaps from that upward elemental surge begun by anthropoid forebears when assumption of the erect posture and binocular vision stimulated their primitive curiosity to the point where consciousness became aware of the need for and devised a means of expressing a sense of pleasure, well-being or joy.

One of the first investigators to delve into the origin of the emotions was Darwin (The Expression of the Emotions in Man and Animals, New York, D. Appleton & Co., 1871). It is now known that expressive behavior is of the greatest importance in relation to normal social conduct, and especially when it occurs abnormally in many mental and organic neurologic conditions. Darwin became curious concerning the evolution of emotional expression in higher animals and as to how it came into being. His three principles are well known, namely, (*a*) the principle of serviceable associated habits, (*b*) the principle of antithesis and (*c*) the principle of actions due to constitution of the nervous system. He endeavored to prove that "expressive behavior" was not evolved as such but served utilitarian purposes and that none of the so-called "muscles of emotion" were developed or modified exclusively for the sake of expression. This idea has been contradicted many times by later students of evolution, who emphasize a case in point, namely, that the vocal muscles, which they claim have always been purely "expressive," are not "utilitarian" in any degree. Darwin expressed the belief that the sneer (as an emotional expression in man) evolved from the utilitarian act of baring the canine tooth preparatory to biting an enemy, but why this type of facial movement persisted after it had lost its original utility he could not explain, although one may now look on it as the hereditary perpetuation of an altered conditioned reflex.

So with the muscular act of laughing. This faculty is now considered as essentially a human perquisite, or at least one belonging also only to the higher apes, and as such is phylogenetically one of the most recent acquisitions by man in his evolutionary progress—if one cares to call it progress. What is laughter? It may be described as a "vent for any sudden joy," but actually it is an involuntary rhythmic contraction of certain respiratory muscles, usually accompanied by certain staccato vocal sounds occurring during exhalation. It is a motor act of the respiratory apparatus that may involve many muscles of the body. Laughter varies in degree from the merest smile through tittering and giggling to hysterical and convulsive bouts that lead to complete exhaustion. Tears are always an accompaniment of prolonged laughter and demonstrate further the close relationship of the antithetical acts of laughing and crying. Both of these reactions serve many useful physiologic purposes, especially as an outlet for emotional tension which needs release and which, if suppressed too long, tends to find a "way out" that may do injury to the personality. Who has not felt the painful tension that perforce ensues when one is aware of an intensely ludicrous situation in one's immediate presence and at the same time is restrained by social propriety from giving way to laughter? One will remember the relief obtained when one is able at last to "let go" and have a good laugh. Or one may recall the similar reaction that occurs when one restrains grief for an appreciable time and the relief that is felt when at last one may have "a good cry."

What causes laughter? It is normally a response to a situation that arouses the emotion of being pleased, such as results from tickling or hearing and seeing laughter, and at times is an exultant cry of victory or of scorn. It is now known that there is an endocrine element associated with prolonged laughter, resulting from the energizing activity of the hormones of the adrenal, thyroid and pituitary glands that are poured into the blood stream, along with glycogen from the liver and insulin from the pancreas—the last two substances occasionally waging a battle that results in a state of exhaustion due to hypoglycemia.

Man clings to the old ideas of the omnipotence and superiority of "genus Homo" in believing that he is the only animal that really laughs. That may be so, granted that this expressing of the emotion of "being pleased" is, as in his case, transmitted through the muscles of respiration as a conditioned reflex. But is it not also probable that man's animal friends in the so-called lower brackets of evolutionary development may express the same state of being pleased by conditioned muscular reflexes other than those utilizing respiration? Life for them is usually a serious business—"to kill or be killed." All know that laughing occurring during a foot race, a gymnastic feat or a combat, such as boxing or wrestling, produces more rapid exhaustion and anoxemia than almost any other

single act. It is possible that in the lower animals a less seriously exhausting means of expressing emotion has developed. He who has owned a dog has not failed to notice the unfolding of an expression of pleasure and expectancy when he is being played with and in his play with another dog. The movements of the tail, the position of the ears, the muscles about the eyes and mouth and the attitude of the body demonstrate vividly different emotions. Chimpanzees and other higher apes seem actually to smile and to make real sounds comparable to human laughter. They have powers of mimicry and the ability to create humorous situations. I remember two fully grown but young chimpanzees at the zoo in St. Louis who had a human audience in a gale of laughter at their antics, their *pièce de resistance* being a lock-step parade and dance about the cage, to which they always resorted when the attention of their audience was waning. The play of their facial muscles and the staccato sounds of their voices at such times were highly reminiscent of the human laugh.

Laughter produced by tickling certain parts of the body appears to be a conditioned reflex elicited as a pleasurable and energizing reaction, but undoubtedly it is the altered continuation of a defense mechanism that was vitally active in more precarious and primitive ancestral days. To produce a laugh the tickling must always be done by something or some one other than the person being tickled. Self-tickling will not tend to cause laughter any more than one will be inclined to laugh at his antics when alone. Ticklish points in one's body were undoubtedly developed as a reflex means of defense against sudden attack and for prompt avoidance of injurious contact. Also, the emotional intent to please rather than to hurt must enter into the act of tickling in order to elicit laughter. This response of laughter to tickling becomes, therefore, not a direct but a complexly consciously conditioned reflex act.

The close relationship of the act of laughing to that of crying is well known and is demonstrated by the occurrence of crying instead of laughing when any prolonged or pent-up emotion is suddenly released or on the receipt of good news or escape from grave danger. To follow this analogy, it is frequently observed that the emotional situation that causes laughter or crying, if too long continued, may be metamorphosed into the more primitive reaction of anger. As Shakespeare says in "Much Ado About Nothing": "He both pleases men and angers them, and then they laugh at him and beat him," and, again, in "Coriolanus": "I could weep and I could laugh, I am light and I am heavy." In the reverse order, the cry of anger may resolve itself almost in the same breath into a laugh of triumph or of scorn, as release of tension is obtained through the vanquishing of an enemy. Carveth Read (The Origin of Man and His Superstitions, London, Cambridge University Press, 1920, p. 60) wrote: "The connection with triumph and cruelty seems to be the most intimate connection of original laughter." Hartley (Priestley, C.: Hartley's Theory of the Human Mind, London, J. Johnson, 1775, p. 271) noted that the first occasion of laughter in a child is a "surprise" which brings momentary fear and then momentary joy in consequence of the removal of that fear. This original experience is then multiplied by imitation, and as "awareness" increases the fixedness of the reflex of laughing increases and becomes integrated as a personality component. This act may then be stimulated into being by the comfort of a bottle of warm milk, a full stomach, the possession of a favorite toy or the attainment of success in the first effort of walking.

As regards the situations which stimulate laughter, one has reference to wit and humor, jest and satire. As laughter becomes more predominantly a sign of mere amusement, it tends to conceal its original purpose. Wit is especially apt to share in the tradition of brutality, to be unkind and to hurt. Wit attempts to restore the laugh of triumph by resorting to concealed attack. Wit, by the same token, may be a personality trait of the psychopath. The essentially cruel, unmoral psychopath is frequently a wit, so-called. The paranoid and the intellectual manic personality and the patients with a toxic endocrine reaction of the hyperthyroid or gonad type belong in this classification. A witticism is considered to be purposeful and is defined by Webster as a "sudden and ingenious association of ideas and words causing surprise or merriment, and depends upon the ability of the

perpetrator to quickly perceive the unusual and unperceived analogies between things." Wit must be sudden, keen, brief and severe. Many of the subtle jokes of today obtain their "thrust" from the element of wit they contain. Sidney Smith, the famous British wit, remarked that he had led his life like a razor, "always in hot water or in a scrape."

Humor, in contrast to wit, is considered to be deeper, more thoughtful, more sustained and kindlier.

The ability to produce real satire is an unusual trait and is closely allied to the sadistic tendencies of the psychopathically degenerate. Not all satirists are abnormal, but some moral degenerates among the intelligentsia are satirical. It is well known that alcohol has an unusual effect on the psychopath, and, by the same token, it is natural that some of the well known satirists have become addicted to the excessive use of stimulants. Dr. Samuel Johnson recorded in verse when he was 29 years old:

> "Of all the griefs that harass the distressed
> Sure the most bitter is a scornful jest,
> Fate never wounds more deep the generous heart
> Than when a blockhead's insult points the dart."

Compared with the number of humorists that have regaled the world with amusement, the number of real satirists is small. Some historians have attributed the flowering of the satirical mind to the Greeks, but undoubtedly the greatest satirical intellects in the world's history developed during the glory of ancient Rome. Horace and Juvenal were two great satirists of that time, and "Erasmus," as he called himself, who first saw light in 1467, did much with the natural asset of capacity for satire which has been compared to "the flashing lightning, terrifying the evil-doer, whilst at the same time it purifies the air." Boileau, Dryden, Dean Jonathan Swift, Pope, Burns, Byron and Voltaire are some of the illustrious men whose satirical shafts were prompted as much by "disease below the diaphragm" as by the background of a sadistic personality.

The "censor control" of laughter is occasionally affected by disease or other abnormal mental states. The high grade feebleminded person is amused by and laughs heartily without restraint at almost anything. The presence of incipient mental disease is frequently first divulged by the unleashing of restraint of laughter, as in dementia praecox, mania and dementia paralytica. On the other hand, inhibition of the laugh response is in some instances the initial symptom of an insidiously developing disaster, such as melancholia, exhaustive psychoneurosis or deficiency of the endocrine system, such as myxedema, cretinism or a hypopituitary or gonadal syndrome.

Failure to inhibit the laughing or crying reflex act or complete or incomplete suppression of the motor component of these acts is frequently noted in organic disease of the central nervous system. Involuntary laughing or crying is noted in vascular or "space-taking" lesions involving the mesencephalon or thalamencephalon. Nearly all patients with so-called double hemiplegia associated with the syndrome of "pseudobulbar palsy" exhibit the reaction of reflex crying or laughing. In many instances the patient will certify that he does not "feel the emotion" that his motor act implies or that he "feels" the reverse emotion; i. e., he will laugh when he is sad and cry when he is happy. This reaction is also common in unilateral hemiplegia with aphasia and symptoms of irritation of the thalamus, especially when due to syphilitic endarteritis—the so-called "syphilitic palsy of early life." It has been observed that in catastrophies to the brain due to vascular disease the tendency is much more toward reflex crying than reflex laughing. On the other hand, the reflex laugh is more likely to occur with a space-taking lesion or degeneration involving the mesencephalon or the tegmentum. This reaction is not unusual in cases of advanced multiple sclerosis, postencephalitic parkinsonism, lesions of the lenticular nucleus group and tumor of the mesencephalon. In the wards of the Philadelphia General Hospital many cases have been studied in which the syndrome of involuntary laughing and crying was exhibited. Many observers, among whom are Spiller, Mills, Kinnier Wilson and

Nonne, have also reported cases of patients who exhibited voluntary nonemotional control of the facial muscles but involuntary paralysis of expression when the emotional stimulus of joy or grief should be demonstrated. Kinnier Wilson (*J. Neurol. & Psychopath.* **4**:299 [Feb.] 1924) reported a case of tumor of the left side of the midbrain which interfered with the nonvolitional faciorespiratory path through the tegmentum on that side in which this unusual reversal of reaction occurred.

The question arises as to whether there is any direct relationship between the emotional factor and the organic pathologic state in the distorted behavior just mentioned. The James-Lange theory of the emotions, which for many years was an accredited hypothesis, presupposed that emotion is the result of "cause and effect" plus an intermediate "something" that lay between the two. It was argued that if the bodily symptoms of rage (such as flushing of the skin, clenching the fists and teeth and tensing of all musculature) were removed, the subject could feel no rage. Sherrington (The Integration Action of the Nervous System, New York, Charles Scribner's Sons, 1906, p. 260) disproved the accuracy of this theory by experiments on dogs in which he removed completely the sensibility of all the viscera and the skin and muscles behind the shoulders; yet the emotional reactions of the animals remained as strong as ever.

In retrospect, may one venture the timid opinion that "it is to laugh" when one takes too seriously one's efforts to unravel the mysteries of that most intricate piece of vital machinery known as "a human being." It is sufficient to say that man is "fearfully and wondrously made" and that undoubtedly the attributes of crying and laughing are the last and most interesting attainments bequeathed by evolution which have contributed so much to the aspect of life that is called the "joy of living."

Book Reviews

Otologische Diagnostik der Hirntumoren. By Dr. Hans Brunner. Paper. Price not given. Pp. 285, with 54 illustrations. Berlin: Urban & Schwarzenberg, 1936.

This book is a series of monographs on a group of subjects equally interesting to the neurologist, the neurosurgeon, the neuropathologist and the otologist. The virtues of the book are that it avoids all didactic dogmatism, that it does not elaborate on any second hand information already contained in the literature but gives the literature briefly and that it is based entirely on the author's own observations of clinical and pathologic material. It is replete with new and original data. The clinical histories are concise and to the point, and the pathologic descriptions, which include histopathologic descriptions of the inner ear, the petrous bone and the brain, especially of the metencephalic and mesencephalic centers of the eighth nerve, are accurate and clear. The author's observations are illustrated by fifty-four figures, most of which are photomicrographs.

The first chapter deals with the changes of the inner ear and the petrous bone in association with increased intracranial pressure. Though in cases of acute increase of intracranial pressure, hyperemia, hemorrhages and edema may characterize the picture clinically and pathologically, as in the case of "choked ear," the absence of changes in association with chronic increase of intracranial pressure, unless combined with local pressure, shows that the mechanisms involved are fundamentally different from those in the eye. In a case of cerebellar tumor, an adhesion of the pia-arachnoid to the saccus endolymphaticus was observed. In chapters 3, 4 and 5 the various changes of the petrous bone in association with tumor of the eighth nerve are described. Chapters 6 and 7 give the diagnosis and differential diagnosis of tumor of the eighth nerve as compared with cystic arachnoiditis, cystic hyperplasia of the lateral recess, meningioma and glioma. Brunner discusses the history, subjective symptoms, especially tinnitus and vertigo, examination of spontaneous nystagmus, disturbances of equilibrium, gait and pointing, caloric and galvanic examination and examination in the turning chair, as well as roentgenographic findings. These findings are correlated with observations made at biopsy, operation and postmortem examination. Brunner points to the fact that roentgen examination sometimes fails to show prolongations of the tumor into the massive central part of the petrous bone. Sometimes the inner auditory canal appears narrowed instead of dilated on the side of the tumor, owing to exostoses, by new formation of bone in the vicinity of the tumor. Sometimes the inner auditory canal may be dilated on the normal side, owing to hydropic edema of the sheaths of the eighth nerve.

Chapters 8 and 9 are the most interesting from a neuropathologic and neuroanatomic point of view. They give complete clinical and neuropathologic descriptions of six cases of deafness in association with tumor of the midbrain.

Chapter 10 contains clinical and anatomic observations on internal hydrocephalus; chapters 11 and 12, on cerebellar tumor. Chapter 13 deals with the problem of labyrinthine hyperexcitability. Chapter 14 discusses the influence of cortical innervation on labyrinthine nystagmus. Chapter 15 gives the results of caloric examination of the labyrinth in cases of tumor of the brain. The labyrinthine hyperexcitability in cases of infratentorial tumor (present in 56 per cent) is interpreted as due to direct stimulation of the medullary vestibular centers and is mostly unilateral or predominates on one side; later it may change into hypoexcitability (in 12 per cent of the cases). The hyperexcitability of the labyrinths in cases of supratentorial tumor (found in 37 per cent) is considered as probably due to interference with the cortical centers of gaze and is most frequently bilateral; it never changes into hypo-excitability. In chapter 17 Brunner gives the results of simultaneous bilateral caloric examination of the labyrinth, which he recommends and considers more significant than comparing the results of separate unilateral calorization.

Study of this book is recommended to all interested in the clinical study and pathologic picture of intracranial neoplasms.